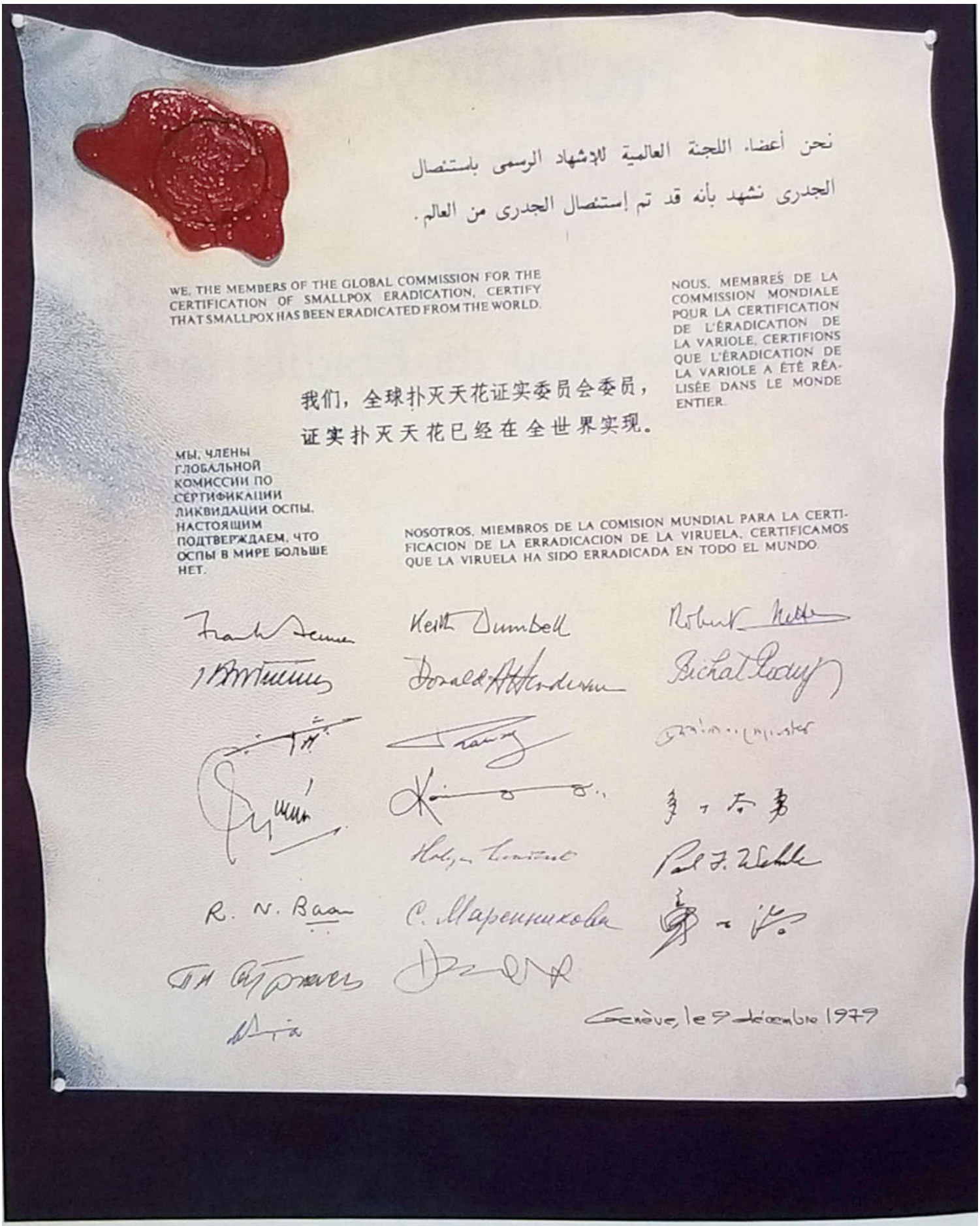
SMALLPOX
and its Eradication

F. Fenner • D. A. Henderson
I. Arita • Z. Ježek • I. D. Ladnyi

WORLD HEALTH ORGANIZATION
Geneva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WE, THE MEMBERS OF THE GLOBAL COMMISSION FOR THE CERTIFICATION OF SMALLPOX ERADICATION, CERTIFY THAT SMALLPOX HAS BEEN ERADICATED FROM THE WORLD.

NOUS, MEMBRES DE LA COMMISSION MONDIALE POUR LA CERTIFICATION DE L'ÉRADICATION DE LA VARIOLE, CERTIFIONS QUE L'ÉRADICATION DE LA VARIOLE A ÉTÉ RÉALISÉE DANS LE MONDE ENTIER.

我们，全球扑灭天花证实委员会委员，
证实扑灭天花已经在全世界实现。

МЫ, ЧЛЕНЫ ГЛОБАЛЬНОЙ КОМИССИИ ПО СЕРТИФИКАЦИИ ЛИКВИДАЦИИ ОСПЫ, НАСТОЯЩИМ ПОДТВЕРЖДАЕМ, ЧТО ОСПЫ В МИРЕ БОЛЬШЕ НЕТ.

NOSOTROS, MIEMBROS DE LA COMISION MUNDIAL PARA LA CERTIFICACION DE LA ERRADICACION DE LA VIRUELA, CERTIFICAMOS QUE LA VIRUELA HA SIDO ERRADICADA EN TODO EL MUNDO.

Keith Dumbell

Donald A. Henderson

R. N. Baar

Genève, le 9 décembre 1979

The official parchment certifying the global eradication of smallpox, 9 December 1979.

Smallpox and its Eradication

F. Fenner, D. A. Henderson,
I. Arita, Z. Ježek, I. D. Ladnyi

World Health Organization
Geneva

THE AUTHORS

Frank Fenner, M.D., has been a professor at the Australian National University since 1949. Since 1969 he has been a member of the WHO Informal Group on Monkeypox and Related Viruses and of various WHO committees on orthopoxviruses, and in 1978–1979 was Chairman of the Global Commission for the Certification of Smallpox Eradication. He is currently a Visiting Fellow in the John Curtin School of Medical Research, Australian National University, Canberra.

Isao Arita, M.D., worked for the smallpox eradication programme in western Africa in 1962–1963 as a member of the staff of the WHO Regional Office for Africa. In 1964 he was transferred to WHO Headquarters in Geneva, and in 1966 he joined the Smallpox Eradication unit, of which he was Chief from 1977 until 1984. He is now Director of the Kumamoto National Hospital in Japan and a member of the advisory group on international health of the Ministry of Health and Welfare of Japan.

Donald Ainslie Henderson, M.D., while at the Communicable Disease Center in the USA, was responsible in 1965–1966 for the planning of the western and central African smallpox eradication–measles control programme, conducted with the support of the United States Agency for International Development. From 1966 to 1977 he was Chief of the Smallpox Eradication unit in the World Health Organization. In 1977 he became Dean of the Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland, USA, and Professor of Epidemiology and International Health. He was a member of the Global Commission for the Certification of Smallpox Eradication.

Zdeněk Ježek, M.D., joined the field staff of the Intensified Smallpox Eradication Programme in 1972, working first with the WHO Smallpox Eradication and Epidemiological Advisory Team in the WHO South-East Asia Region and later in Somalia. He joined the Smallpox Eradication unit at WHO Headquarters in 1980 and became Chief of the unit in 1985.

Ivan Danilovich Ladnyi, M.D., served as a WHO Intercountry Adviser on smallpox eradication in Africa from 1965 to 1971. From 1976 to 1983 he was Assistant Director-General of the World Health Organization, responsible for communicable and parasitic diseases. He was then Deputy Director of the All-Union Institute of Medical Information of the Ministry of Health of the USSR from 1983 until his death in 1987.

The authors alone are responsible for the views expressed in this publication.

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Foreword

For more than three thousand years, smallpox was a major scourge of mankind, spreading across the world as new centres of population became established and grew in size. Because of its high fatality rate, it was universally feared; in the towns and cities of Asia and Europe where records were kept, it caused on average 10% of all deaths each year. As early as the tenth century, Chinese and Indian sages had discovered a method that provided some protection against this terrible scourge, albeit one which often resulted in serious illness and some loss of life. This was the inoculation of smallpox virus from scabs—variolation—a practice that was taken up in a number of countries but seldom widely applied. Then in 1796 came one of the seminal discoveries of medicine—the demonstration by experiment that a harmless virus obtained from cows could protect man against smallpox. Edward Jenner, an English country doctor, had discovered vaccination—a practice which was rapidly disseminated throughout the world. It resulted in a marked decrease in the toll of smallpox in the industrialized countries, but the disease continued almost unabated in Africa, Asia and Latin America.

The World Health Organization was established in 1948 and from its inception successive World Health Assemblies urged Member States to take all measures to control smallpox. In 1953 the first Director-General, Dr Brock Chisholm, made an unsuccessful attempt to persuade the World Health Assembly to undertake a global smallpox eradication programme. Five years later a Soviet delegate to the Assembly, Dr Viktor Zhdanov, persuaded the Organization to accept responsibility for a global eradication programme. But only minimal funds were provided, and although by 1967 the disease was eliminated from some thirty countries in Asia, Africa and South America, the hard core of the problem—the Indian subcontinent and most countries in sub-Saharan Africa—was largely unaffected.

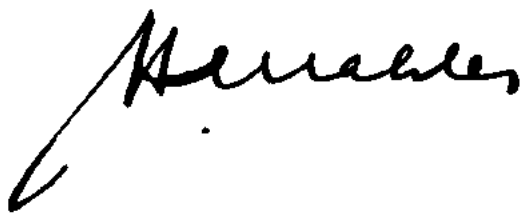
In 1966 the World Health Assembly decided that this situation was intolerable, and established an Intensified Smallpox Eradication Programme, with an annual allocation of $2.4 million from the WHO regular budget and the declared goal of global eradication within 10 years. Thanks to the efforts of numberless national health staff in the endemic countries, the enthusiastic devotion of international workers, and the masterly coordination of the effort by the WHO Smallpox Eradication unit, the goal of global eradication was achieved in just over ten years.

Simultaneously, a sustained effort was made to demonstrate to the public and the international health community that eradication had indeed been achieved, by a carefully orchestrated certification programme planned and coordinated by the World Health Organization. The result was that on 8 May 1980 the Thirty-third World Health Assembly adopted a resolution declaring that smallpox had been eradicated globally. In another resolution it endorsed 19 recommendations covering all aspects of the post-smallpox-eradication era, including the cessation of vaccination of the public and of international travellers. Despite intensive surveillance, no case of endemic smallpox has been detected anywhere in the world since the last case in Somalia in October 1977.

The Thirty-third World Health Assembly recommended that this unique accomplishment should be properly recorded; this book is the result. Written by five men who were intimately associated with various aspects of the eradication and certification programmes, and subject to detailed review by many of their colleagues

in the eradication campaign, it provides a comprehensive description of a formerly cosmopolitan and lethal disease that man has now eradicated, forever, and of the programme in some eighty countries in Africa, Asia and South America that led to this achievement. The major part of the book recounts the saga of eradication in the ancient strongholds of the disease—Africa, the Indian subcontinent and other parts of Asia. Also included are descriptions of other poxvirus infections of man, and a detailed description of a new, generalized orthopoxvirus disease of man, human monkeypox, discovered during the smallpox eradication programme. The book concludes with an overview of the lessons learnt during the programme—lessons that have already been applied by the World Health Organization to a variety of other programmes designed to lighten the burden of human illness, from the Expanded Programme on Immunization to the new efforts on AIDS.

The World Health Organization, and I, as its Director-General, are proud of this signal achievement in preventive medicine, and proud of the book in which it is described, with its wealth of detail and colour plates, figures, maps and graphs, that records for posterity just what this extinct disease was like and describes in graphic terms the problems and successes of the Intensified Smallpox Eradication Programme.



H. Mahler, M.D.
Director-General

Preface

The world's last naturally occurring case of smallpox developed illness in Somalia late in October 1977; the last case, which was associated with a laboratory infection, occurred in England in September 1978. Following an extensive programme to verify the absence of the disease, the Thirty-third World Health Assembly in May 1980 adopted a resolution accepting the report of the Global Commission for the Certification of Smallpox Eradication, and affirming its belief that this once-universal disease had been eradicated world-wide. In the resolution, the Health Assembly requested "the Director-General to ensure the production, within a reasonable period of time, of appropriate publications describing smallpox and its eradication, in order to preserve the unique historical experience of eradication and thereby contribute to the development of other health programmes". This book, published by the World Health Organization, responds to this request. The authors, all of whom were personally involved in the programme's execution, are, however, entirely responsible for the opinions expressed.

Preparation of the book began in 1980 and was completed in 1987. It was a truly collaborative effort, and each of the authors reviewed and commented on all chapters at various stages of their preparation. Dr Fenner was responsible for the overall organization of the book, the reference lists and the indexes, and wrote Chapters 1–6, 8, 29 and 30. Dr Henderson wrote Chapters 9, 10, 12–22 and 31, assisted by Dr Ježek, who assembled and drafted basic material from the WHO Smallpox Archives and elsewhere. Dr Arita prepared the drafts of Chapters 7, 11 and 23–28 for further editing by Dr Fenner.

The four authors just named wish to pay special tribute to their co-author, Dr Ivan D. Ladnyi, whose tragic death in March 1987 prevented him from contributing, to the later stages of the preparation of this book, the full wealth of his knowledge and experience of the Intensified Smallpox Eradication Programme. His experience was especially valuable as he had both participated actively in the field work in Africa and provided staunch support and leadership in his later position as Assistant Director-General of the World Health Organization.

In addition to review of each chapter by each of the authors, 78 other persons, who were experts in an appropriate scientific field or who had personal knowledge of a particular eradication or certification programme, commented on various chapters when they were in draft form. Their names and affiliations are listed in the Acknowledgements.

The Intensified Smallpox Eradication Programme, the description of which is the main focus of this book, involved many people, in many parts of the world. Its successful prosecution depended on a variety of different activities, ranging from field work to administration through laboratory studies and fund-raising. We decided that the book would be most instructive if it incorporated the whole of this spectrum, and this we have endeavoured to reflect. For completeness, we have also provided a full account of the clinical and epidemiological features of the disease, the history of smallpox and of vaccination, and a description of the immunological and virological aspects of smallpox and of vaccination.

The structure of the book is defined by the chapter headings, but it may be useful to elaborate on the rationale of the nature and order of the topics covered. First, we

thought that a well-illustrated description of this now-extinct disease should be provided, so that readers would understand the nature of what was one of man's most serious diseases (Chapter 1). Then, since smallpox was caused by one virus and was eradicated through use of a vaccine which was prepared from another, related virus, there are chapters on the virology, pathology, pathogenesis and immunology of orthopoxvirus infections in general and smallpox in particular (Chapters 2 and 3). The other basic science crucial to smallpox eradication was epidemiology (Chapter 4), since eradication could not have been achieved without adequate understanding of how the disease was transmitted or if an animal reservoir had been present.

Following these four technical chapters, smallpox and its control are set in their historical perspectives in Chapters 5–8. The long and fascinating history of smallpox is summarized in Chapter 5, which deals with the history of smallpox from ancient times until the end of the 19th century, and in Chapter 8, which is concerned with its extent and incidence between 1900 and 1958, when global eradication was first proposed in the World Health Assembly. Likewise of interest is the history of the methods used to mitigate the severity of smallpox (variolation) and to prevent the disease (vaccination), which antedate other methods for successful intervention in infectious diseases. Thus Chapter 6 describes the early use of variolation and the introduction of vaccination, from the time of its discovery by Edward Jenner until the end of the 19th century. The fourth historical chapter (Chapter 7) traces developments in smallpox vaccine and vaccination up to 1958.

The succeeding 15 chapters describe various aspects of the global eradication campaign. Chapter 9 explores the development and application of the concept of eradication, the events which led to the resolution in the World Health Assembly in 1959 that global smallpox eradication be undertaken, the progress that was made in this effort between 1959 and 1966, and finally the circumstances which culminated, in 1966, in a decision to begin an intensified programme. Chapter 10 summarizes major events and developments in the Intensified Smallpox Eradication Programme throughout its course, from 1967 to 1980, and provides a perspective for subsequent chapters, which deal with operations in different parts of the world. It concludes with a series of maps of the world, graphs, and accompanying text, which encapsulate the history of this period. The provision of adequate amounts of a potent and stable vaccine and the development of better methods of vaccination were of such central importance to the Intensified Smallpox Eradication Programme that Chapter 11 is devoted in its entirety to these topics.

Chapters 12–22 describe the actual operations of the Intensified Smallpox Eradication Programme in different parts of the world on a geographical basis, corresponding, in large part, to the temporal sequence in which they were begun or strengthened. Because of travel between the endemic countries and their neighbours, as well as between them and more distant industrialized countries (from which endemic smallpox had been eliminated by 1950) there were many importations, some with serious consequences. Chapter 23 is devoted to this subject and to infections which occurred in laboratories.

The programme involved not only the eradication of smallpox, but also an array of activities designed to provide the world community with the necessary level of assurance that smallpox had indeed been eradicated. Without this, national health services would not have agreed to discontinue the vaccination of their own populations, nor would they have accepted the proposal that international travellers should be admitted without a valid vaccination certificate. Chapters 24–27 review the methods employed to certify that smallpox eradication had been accomplished, as well as observations made during the certification process.

In 1980, when the Thirty-third World Health Assembly proclaimed the achievement of global eradication, it adopted 19 recommendations made by the Global Commission for the Certification of Smallpox Eradication, for activities to

be conducted in the post-eradication era—from 1980 until the publication of this book. Chapter 28 describes the implementation of these recommendations. This is followed by a chapter detailing the investigations which were undertaken to determine the nature and public health importance of human monkeypox, the smallpox-like disease that was discovered during the eradication campaign in Africa. Chapter 30 looks again at the virology and epidemiology of smallpox, to answer—with confidence—questions about its possible recurrence or return as a human disease. The book concludes with a chapter which attempts to fulfil the request of the World Health Assembly that the book should discuss "the principles and methods that are applicable to other programmes", and assesses the costs and benefits of the Intensified Smallpox Eradication Programme.

* *
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In preparing the book, the authors have availed themselves of the extensive published literature and have cited references wherever possible. For activities after 1960, they have relied most heavily on the special smallpox archives that were established in WHO Headquarters in 1980. All data in the eradication and certification chapters not ascribed to a particular source came from these archives. Personal recollections of the authors and others who have been consulted have been regularly corroborated through reference to archival material and consultation with other participants.

We have provided many detailed tables documenting matters such as disease incidence, numbers of vaccinations performed, results of assessments and costs of the programme, in recognition of the fact that few such data have been published and access to them in the WHO archives is difficult. In this sense, the book is, and is intended to be, in part archival in nature. For clarity of exposition, we have liberally supplemented these tables with maps and graphs. We have used illustrations freely, for several purposes. We have endeavoured to include a photograph, either alone or in a group, of many of the more senior persons involved in the eradication programme. We have used colour photographs to illustrate the clinical appearance and relevant virological features of smallpox and other poxvirus diseases, and colour and half-tone prints provide a flavour of the terrain and circumstances under which the campaigns were conducted in different parts of the world.

We hope that this book will enable readers to appreciate the nature and magnitude of the task of global eradication of a once-common human disease; a goal that could not have been achieved without the dedicated contributions of hundreds of international experts and tens of thousands of national health workers, working within a framework of international cooperation provided by the World Health Organization. This book bears testimony to their efforts and a remarkable adventure in public health in which we have been privileged to share.

F. Fenner, D. A. Henderson, I. Arita, Z. Ježek
Geneva, September 1987

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Acknowledgements

In order to ensure that the contents of each chapter were as accurate as possible and provided a properly balanced view of the state of the science or the nature of the operations involved, every chapter was first read critically by all the authors. When these comments and criticisms had been evaluated and incorporated by the primary author concerned, each chapter was sent to a number of reviewers.

The reviewers were people who were judged by the authors to be knowledgeable in the field covered in a particular chapter, as a scientist, as an administrator, or as a person who had been directly involved in a particular facet of the eradication campaign. The responses of the reviewers, whose names and affiliations at the time are listed overleaf, proved most useful; the decision whether to incorporate such comments was made by the author concerned.

In addition to the reviewers, who were most generous with their time and talents, there were many others without whose efforts this book could never have become a reality. The authors wish to acknowledge several in particular. Mr John Wickett of the World Health Organization assumed responsibility for the laborious task of preparing financial analyses, reconciling morbidity data, and compiling and verifying basic data pertaining to vaccine receipts and shipments and many other items of information. He also acted as photo editor, assembling pictures from public and private sources throughout the world and preparing them for publication. To ensure uniformity of style, the diagrams and black-and-white maps were all prepared by one artist, Mr Kevin Cowan of the Australian National University. The maps in full colour were prepared by Miss Susan Hobbs in Geneva. The authors also express their gratitude to Mr Dominic Loveday and Mrs Stella Deck of the World Health Organization for their editorial work on all aspects of the book, and to Mr Loveday and Mr Keith Wynn of the World Health Organization who guided the book through to publication.

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Most of the colour and half-tone illustrations used come from the WHO Smallpox Archives; others were kindly provided by various field and laboratory workers. A few were obtained from other sources, as indicated in the acknowledgements on each plate.

Preparation of so large and complex a book as this was inevitably an expensive task. The authors are grateful to the World Health Organization for providing office facilities and access to the WHO Smallpox Archives for work done in Geneva; the two senior authors are appreciative of the financial assistance provided by the World Health Organization for clerical and technical assistance, and to the Australian National University and the Johns Hopkins University respectively for special office facilities. Finally, both the World Health Organization and the authors are grateful for the financial assistance provided specifically for the production of the book by the Finnish International Development Agency, the International Division, Ministry of Health and Welfare, Japan, and the Japan Shipbuilding Industry Foundation.

Reviewers

A. N. Agle, Centers for Disease Control, Atlanta, Georgia, USA.

M. K. Al Aghbari, WHO Regional Office for the Eastern Mediterranean, Alexandria, Egypt.

C. Algan, WHO Programme Coordinator, Madagascar.

F. Assaad, Division of Communicable Diseases, World Health Organization, Geneva, Switzerland.

R. N. Basu, Directorate of Health Services, New Delhi, India.

D. Baxby, Department of Medical Microbiology, University of Liverpool, England.

A. S. Benenson, Graduate School of Public Health, San Diego State University, California, USA.

D. B. Bisht, Ministry of Health and Family Welfare, New Delhi, India.

J. B. Blake, National Library of Medicine, Bethesda, Maryland, USA.

J. G. Breman, Centers for Disease Control, Atlanta, Georgia, USA.

L. B. Brilliant, Network Technologies International, Ann Arbor, Michigan, USA.

S. J. Brown, Management Sciences for Health, Washington, DC, USA.

P. Carrasco, Expanded Programme on Immunization, Pan American Health Organization/WHO Regional Office for the Americas, Washington, DC, USA.

A. B. Christie, formerly Head, Department of Infectious Diseases, University of Liverpool, England.

M. L. Clements, Department of International Health, Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland, USA.

J. Cohen, World Health Organization, Geneva, Switzerland.

J. S. Copland, Expanded Programme on Immunization, World Health Organization, Geneva, Switzerland.

A. W. Downie, formerly Professor of Bacteriology, University of Liverpool, England.

K. R. Dumbell, formerly Professor of Virology, St Mary's Hospital Medical School, London, England.

J. J. Esposito, Centers for Disease Control, Atlanta, Georgia, USA.

S. O. Foster, Centers for Disease Control, Atlanta, Georgia, USA.

D. P. Francis, Centers for Disease Control, Atlanta, Georgia, USA.

N. C. Grasset, Epidemiologist, Douvaine, France.

V. T. H. Gunaratne, formerly Director, WHO Regional Office for South-East Asia, New Delhi, India.

A. C. Hekker, National Institute of Public Health, Bilthoven, Netherlands.

R. H. Henderson, Expanded Programme on Immunization, World Health Organization, Geneva, Switzerland.

D. Heymann, Centers for Disease Control, Atlanta, Georgia, USA.

R. Hogan, Diarrhoeal Diseases Control Programme, World Health Organization, Geneva, Switzerland.

D. R. Hopkins, Centers for Disease Control, Atlanta, Georgia, USA.

A. Horwitz, formerly Director, Pan American Health Organization/WHO Regional Office for the Americas, Washington, DC, USA.

Z. Islam, WHO Programme Coordinator, Hanoi, Viet Nam.

T. S. Jones, Centers for Disease Control, Atlanta, Georgia, USA.

C. Kaplan, Department of Microbiology, University of Reading, England.

L. A. Kaprio, formerly Director, WHO Regional Office for Europe, Copenhagen, Denmark.

J. Keja, Expanded Programme on Immunization, World Health Organization, Geneva, Switzerland.

C. H. Kempe, formerly Professor of Pediatrics and Microbiology, University of Colorado, Denver, Colorado, USA.

L. N. Khodakevich, Smallpox Eradication unit, World Health Organization, Geneva, Switzerland.

J. P. Koplan, Centers for Disease Control, Atlanta, Georgia, USA.

J. Kostrzewski, Medical Section, Polish Academy of Sciences, Warsaw, Poland.

A. D. Langmuir, formerly Director, Epidemiology Branch, Center for Disease Control, Atlanta, Georgia, USA.

R. R. Lindner, WHO Regional Office for the Western Pacific, Manila, Philippines.

S. K. Litvinov, World Health Organization, Geneva, Switzerland.

H. B. Lundbeck, National Bacteriological Laboratory, Stockholm, Sweden.

G. I. Lythcott, City University of New York Medical School, New York, USA.

W. H. McNeill, Department of History, University of Chicago, Illinois, USA.

S. S. Marennikova, Moscow Research Institute for Viral Preparations, Moscow, USSR.

G. Meiklejohn, formerly Professor of Medicine, University of Colorado, Denver, Colorado, USA.

J. D. Millar, National Institute of Occupational Safety and Health, Atlanta, Georgia, USA.

G. Miller, Institute of the History of Medicine, Johns Hopkins University, Baltimore, Maryland, USA.

L. Morris, Centers for Disease Control, Atlanta, Georgia, USA.

W. H. Mosley, Institute for International Programs, Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland, USA.

S. I. Music, Centers for Disease Control, Atlanta, Georgia, USA.

J. H. Nakano, Centers for Disease Control, Atlanta, Georgia, USA.

R. Netter, National Health Laboratory, Paris, France.

D. P. Olsen, Centers for Disease Control, Atlanta, Georgia, USA.

A. Omar, formerly Minister of Health, Kabul, Afghanistan.

M. J. O'Regan, formerly Leprosy unit, World Health Organization, Geneva, Switzerland.

G. T. Presthus, WHO Expanded Programme on Immunization, Sana'a, Yemen.

C. C. A. de Quadros, Expanded Programme on Immunization, Pan American Health Organization/WHO Regional Office for the Americas, Washington, DC, USA.

A. R. Rao, formerly Medical Superintendent, Infectious Diseases Hospital, Madras, India.

K. Raška, formerly Director, Division of Communicable Diseases, World Health Organization, Geneva, Switzerland.

J. K. Sarkar, formerly Professor of Virology and Director, School of Tropical Medicine, Calcutta, India.

M. Sathianathan, WHO Programme Coordinator, Bangkok, Thailand.

E. O. Shafa, Expanded Programme on Immunization, World Health Organization, Geneva, Switzerland.

M. I. D. Sharma, formerly Commissioner of Rural Health, New Delhi, India.

M. P. Siegel, formerly Assistant Director-General, World Health Organization, Geneva, Switzerland.

J. Sulianti Saroso, formerly Director-General for the Control and Prevention of Communicable Diseases, Ministry of Health, Indonesia.

D. J. M. Tarantola, Division of Epidemiological Surveillance and Health Situation and Trend Assessment, World Health Organization, Geneva, Switzerland.

Y. Tekeste, Office of the National Committee for Central Planning, Addis Abeba, Ethiopia.

J. L. Tulloch, Diarrhoeal Diseases Control Programme, World Health Organization, Geneva, Switzerland.

N. A. Ward, Expanded Programme on Immunization, WHO Regional Office for the Eastern Mediterranean, Alexandria, Egypt.

W. C. Watson, Centers for Disease Control, Atlanta, Georgia, USA.

P. F. Wehrle, Department of Pediatrics, Los Angeles County–University of Southern California Medical Center, Los Angeles, California, USA.

K. L. Weithaler, formerly WHO Expanded Programme on Immunization, Kabul, Afghanistan.

J. F. Wickett, Smallpox Eradication unit, World Health Organization, Geneva, Switzerland.

R. J. Wilson, formerly Scientific Director, Connaught Laboratories, Toronto, Canada.

V. M. Zhdanov, Ivanovsky Institute, Moscow, USSR.

P. Ziegler, Expanded Programme on Immunization, WHO Regional Office for South-East Asia, New Delhi, India.

CHAPTER 1

THE CLINICAL FEATURES OF SMALLPOX

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INTRODUCTION

As this book went to press, endemic smallpox had been eradicated from Europe and North America for almost half a century and from the populous countries of China and India for some 25 and 10 years respectively. The majority of people—including the majority of physicians—now living have never seen a case of this once-dreaded disease. What was it like? For the physician, what were its clinical features and its complications? What factors influenced the prognosis? What diseases entered into its differential diagnosis? Nowhere is there a better answer to these questions than in the book written by Ricketts and illustrated by Byles over three-quarters of a century ago (Ricketts, 1908).

Since then, however, long series of carefully studied cases of both variola major (Rao, 1972) and variola minor (Marsden, 1936) have been documented, and laboratory investigation has become a powerful tool for confirmation of the diagnosis in puzzling cases. Further, during the global smallpox eradication programme a large number of WHO epidemiologists and their national counterparts had extensive experience of smallpox as it occurred in the field in urban and rural areas and among nomads, as distinct from the hospitals from which Ricketts's, Rao's and Marsden's material was drawn. However, only limited clinical studies were possible in rural situations, outside of hospitals. The most comprehensive clinical study of variola major in a non-hospital setting is a series of 539 cases seen in their houses in Pakistani Punjab in 1966–1967 (Mack et al., 1970). Where relevant, data from this study will be used to supplement the description of hospital-based cases described by Rao (1972). An attempt has been made to interpret the symptoms in the light of current understanding of the pathogenesis and immunology of orthopoxvirus infections, as outlined in Chapter 3.

The plan of the present chapter follows Ricketts in that the account of the clinical features of smallpox consists mainly of a description of the rash, based on photographs of patients, most of which were prepared during the global smallpox eradication programme. Because smallpox is now extinct, we have to take the unusual step, in the clinical description of a human disease, of referring to it in the past tense; this was previously the case only with diseases that apparently disappeared and could be identified only by contemporary descriptions, such as the "English sweat", or the "sweating sickness".

JOYCE GREEN HOSPITAL, DARTFORD, ENGLAND

Plate 1.1. Thomas Frank Ricketts (1865-1918). Medical Superintendent of the Smallpox Hospitals and of the River Ambulance Service of the Metropolitan Asylums Board, London. His book on the clinical features of smallpox was based on the personal examination of many thousands of cases of variola major.

VARIETIES OF SMALLPOX

From the time it was first recognized as a distinct disease until about the end of the 19th century, smallpox was regarded as a uniformly severe disease, associated with a high case-fatality rate, in every part of the world. Mild cases and even mild outbreaks of smallpox were occasionally mentioned in the old literature, but they were the exception; nowhere did endemic mild smallpox occur. Smallpox was designated by many names in various languages, but no one saw a need to distinguish different varieties of smallpox, although the existence of different clinical types (see below) was recognized from the time of Thomas Sydenham (1624–1689) in Europe and much earlier in India and China.

The situation changed when Korté (1904) described a very mild smallpox-like disease, with a case-fatality rate of 1% or less in unvaccinated persons, that had occurred in South Africa for several years and was known locally as kaffir-pox, or "amaas", a word of uncertain origin, possibly a corruption of the Dutch word *masels* or *mazelen* (measles) (Dixon, 1962). Subsequently, Chapin (1913, 1926) recognized that a similar mild disease had been occurring in North America since about 1896, and had subsequently been exported from there to South America, Europe and Australia. There was controversy about the relationship of this disease to smallpox until the mid-1950s (Jong, 1956), but virological studies (see Chapter 2) showed that there was no doubt that "amaas" and "alastrim" (from the Portuguese *alastra*, something which "burns like tinder, scatters, spreads from place to place"), as it was called in South America, were indeed mild varieties of smallpox. Although many other names were used, this clinico-epidemiological variety of smallpox has come to be called "variola minor", a designation that led to the use of the term "variola major" for "classical" smallpox.

Recent studies of viral strains recovered from outbreaks of variola minor in various countries have shown that they fall into two groups distinguishable by biological properties, one consisting of strains derived from outbreaks in South America or traceable to an American source (which we shall call "alastrim" virus) and the other comprising most strains from Africa (see Chapter 2).

During the first half of the 20th century all outbreaks of smallpox in Asia and most of those in Africa were due to variola major (with case-fatality rates of 20% or more in the unvaccinated). Variola minor (with case-fatality rates of 1% or less) was endemic in some countries of Europe and of North and South America and, together with variola major, in many parts of Africa. With the more careful study that began after global eradication had been proclaimed as a goal of WHO in

1959, it was recognized that some outbreaks of smallpox in western, central and eastern Africa and in Indonesia were associated with a lower case-fatality rate than classical variola major, in the range of 5–15% instead of over 20%. Some of these lower figures resulted from aggregating all reported cases in places where both varieties of smallpox were endemic (see Chapter 8), but there were other places where this was not the explanation. The clinical picture of smallpox with a case-fatality rate of 5–15% was indistinguishable from that of variola major, both haemorrhagic and flat types of the disease occurring with about the same frequency as in classical smallpox. Preliminary tests suggested that certain laboratory characteristics of some of the strains recovered from these outbreaks were intermediate between those of variola major and variola minor (see Chapter 4), but later studies failed to support the differentiation of a separate "intermedius" virus. In this book all outbreaks of smallpox will be categorized as either variola major, with case-fatality rates of 5–25% and occasionally more, or variola minor, with case-fatality rates of about 1% or less.

WHO, 1971

Plate 1.2. A. Ramachandra Rao (b. 1917). Formerly Superintendent of the Infectious Diseases Hospital, Madras, India. His book on smallpox was based on the personal study of nearly 7000 hospitalized cases of variola major. He also made important contributions to the understanding of the epidemiology of smallpox in India (see Chapter 15).

THE CLASSIFICATION OF CLINICAL TYPES OF VARIOLA MAJOR

It has long been recognized that several clinical types of variola major could be distinguished which differed in prognosis, differential diagnosis and transmissibility. The old subdivision according to the density of the focal eruption was shown by Dixon (1962) and Rao (1967) to have less prognostic value than a classification based on the nature and evolution of the rash. For this reason a WHO Scientific Group on Smallpox Eradication (1968) adopted the classification proposed by Rao and fully described in his book on smallpox (Rao, 1972). A WHO Expert Committee on Smallpox Eradication (1972) reaffirmed its acceptance of this classification (Table 1.1), according to which the commonest clinical type (ordinary-type smallpox) is subdivided in relation to the density of the rash, since this had prognostic significance. The great majority of cases of variola major seen in hospitals among both unvaccinated and vaccinated persons—88.8% and 70% respectively in Rao's series of 6942 cases

Table 1.1. A classification of clinical types of variola major[a]

Ordinary type	Raised pustular skin lesions. Three subtypes: confluent—confluent rash on face and forearms; semiconfluent—confluent rash on face, discrete elsewhere; discrete—areas of normal skin between pustules, even on face.
Modified type	Like ordinary type but with an accelerated course.
Variola sine eruptione	Fever without rash caused by variola virus; serological confirmation required.
Flat type	Pustules remained flat; usually confluent or semiconfluent. Usually fatal.
Haemorrhagic type	Widespread haemorrhages in skin and mucous membranes. Two subtypes: early, with purpuric rash; always fatal; late, with haemorrhages into base of pustules; usually fatal.

[a] Based on Rao (1972).

Table 1.2. The frequency and case-fatality rates of different clinical types of variola major, according to vaccination status (presence of a scar) in hospitalized patients in Madras[a]

Clinical type	Unvaccinated subjects			Vaccinated subjects		
	Number of cases	Percentage of total	Case-fatality rate (%)	Number of cases	Percentage of total	Case-fatality rate (%)
Ordinary type:	3 147	88.8	30.2	2 377	70.0	3.2
Confluent	808	22.8	62.0	156	4.6	26.3
Semiconfluent	847	23.9	37.0	237	7.0	8.4
Discrete	1 492	42.1	9.3	1 984	58.4	0.7
Modified type	76	2.1	0	861	25.3	0
Flat type	236	6.7	96.5	45	1.3	66.7
Haemorrhagic type:	85	2.4	96.4	115	3.4	93.9
Early	25	0.7	100.0	47	1.4	100.0
Late	60	1.7	96.8	68	2.0	89.8
Total	3 544	—	35.5	3 398	—	6.3

[a] Based on Rao (1972).

(Table 1.2)—were ordinary-type smallpox (and other reported series confirm this); the case-fatality rates in unvaccinated cases with confluent, semiconfluent and discrete rashes were 62%, 37% and 9.3% respectively. Although its use was suggested by Rao, such a subclassification is hardly justified for modified-type or flat-type cases, but it is useful to consider early and late haemorrhagic-type cases separately, since they were probably the results of different pathophysiological processes.

A special comment is required on the designation of cases as vaccinated by both Rao (1972) and other investigators. Until freeze-dried vaccine became available and regular assessment was made of the results of vaccination, many vaccinations, especially in tropical countries, were performed with vaccine of less than the required potency (see Chapter 11). The categorization of a subject as "vaccinated" was made on the basis of the presence of what was regarded as a vaccination scar. The presence of such a scar was, however, not certain evidence of successful vaccination. The rotary lancet, used for vaccination on the Indian subcontinent, was attended by considerable trauma, and sometimes bacterial infection alone could produce scarring. On the other hand, vaccination by the jet injector sometimes resulted in a very small scar which might be overlooked on the skin of subjects bearing many scars of traumatic origin. In spite of these shortcomings, the vaccination scar provided a more easily determined and reliable index of an individual's immune status *vis-à-vis* smallpox than was possible with other infectious diseases.

ORDINARY-TYPE SMALLPOX

The Incubation Period

The incubation period is the interval between the implantation of infectious virus and the onset of the first symptoms, which in smallpox were fever and constitutional disturbances. Determination of the length of the incubation period is discussed in detail in Chapter 4; in exceptional instances the duration, from the time of infection until the onset of fever, was as short as 7 days or as long as 19 days, but in the great majority of cases the period extended over 10–14 days, usually 12 days.

Symptoms of the Pre-eruptive Stage

The incubation period in smallpox was a period of intense activity in terms of viral replication and spread within the body and the development of the immune response (see Chapter 3), of which there was at that time no clinical evidence. It ended when the patient became feverish and ill (Fig. 1.1). The onset of fever and malaise was sudden, the temperature usually rising to between 38.5 °C and 40.5 °C. Other symptoms varied in frequency (Table 1.3). Patients suffering from variola major usually complained of a splitting headache, sometimes frontal but usually generalized, and many complained of severe backache (Rao, 1972). A small proportion of children had convulsions and some adults were delirious at this stage. Vomiting occurred in about half of all patients, and

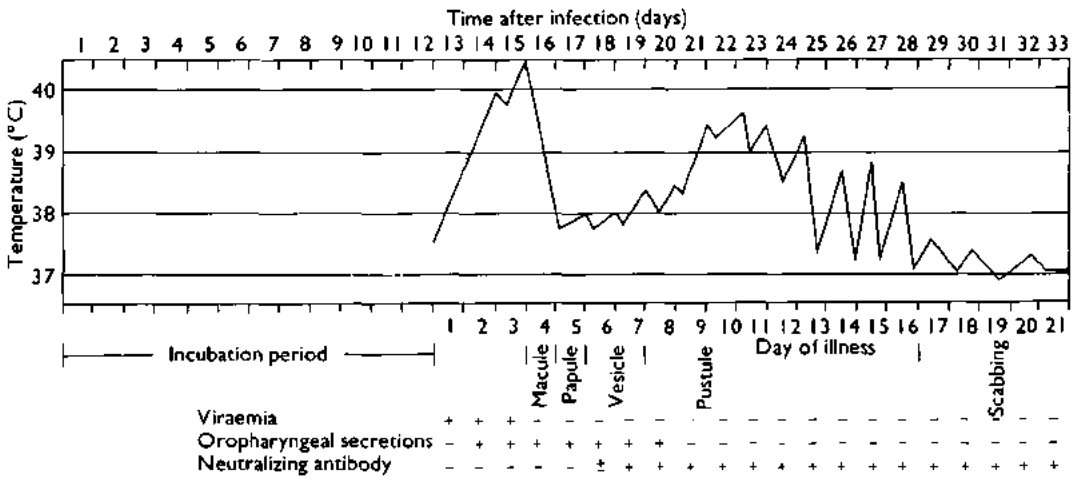

Time after infection (days)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33
Temperature (°C)
40
39
38
37
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Day of illness
Incubation period
Macule
Papule
Vesicle
Pustule
Scabbing
Viraemia
Oropharyngeal secretions
Neutralizing antibody

Fig. 1.1. The clinical course of moderately severe ordinary-type smallpox in an unvaccinated subject: the temperature chart, the development of rash, the presence of virus in the blood and oropharyngeal secretions and the time of appearance of neutralizing antibody in the serum. (Data from various sources.)

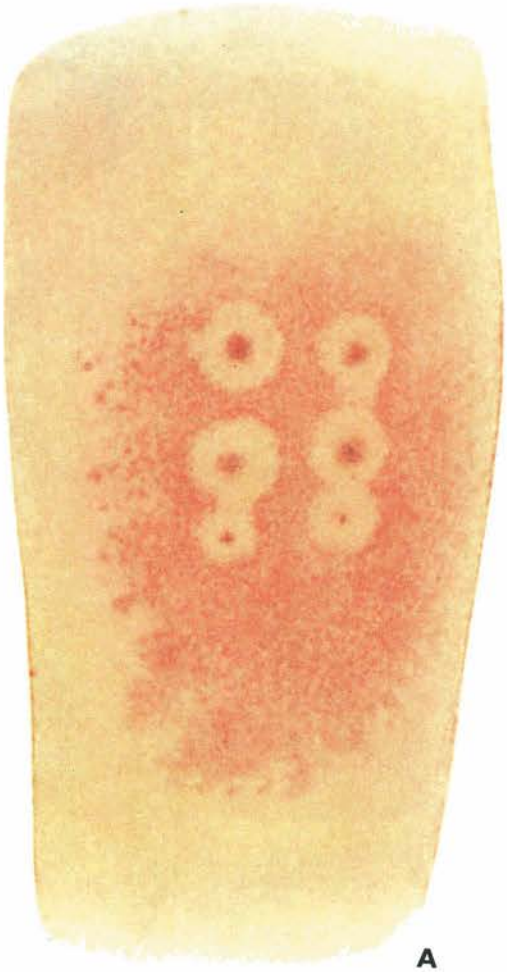
diarrhoea in about 10%. Some suffered abdominal colic, which could lead to a diagnosis of appendicitis. The patient was usually ill, with an appearance of general toxaemia. By the 2nd or 3rd day (rarely the 4th) the temperature had fallen and the patient felt somewhat better; at this time the macular rash appeared.

In older writings (e.g., Ricketts, 1908) there was often reference to the occurrence of an erythematous rash during the pre-eruptive phase (prodromal rash), best seen in fair-skinned subjects (Plate 1.3A and B). Some authors (Dixon, 1962; Rao, 1972) have cast doubt on its occurrence in unvaccinated subjects, but all agree that a fleeting "allergic" rash sometimes occurred in vaccinated individuals, most readily visible around the vaccination scar (see Plate 1.3), in the axillae, behind the knees and in the inguinal region. The erythematous rash common in the early stages of haemorrhagic-type smallpox had to be distinguished from the prodromal rash of ordinary-type or modified-type smallpox.

Table 1.3. Frequency of symptoms (percentages of cases) in the pre-eruptive stage in variola major and variola minor

Symptom	Variola major[a]	Variola minor[a]	
	6942 cases (Rao, 1972)	12 847 cases (Marsden, 1936)	859 cases (Noble et al., 1970)
Fever	100.0	..	98.2
Headache	90.0	75.0	79.4
Malaise	..	..	66.7
Chills	60.0	34.0	62.4
Anorexia	..	..	60.6
Backache	90.0	38.8	44.2
Pharyngitis	15.0	20.6	38.2
Nausea	..	11.0	37.0
Vomiting	50.0	34.2	30.3
Diarrhoea	10.0	..	3.6
Delirium	15.0	..	..
Abdominal colic	13.0	..	..
Convulsions	7.0	..	..

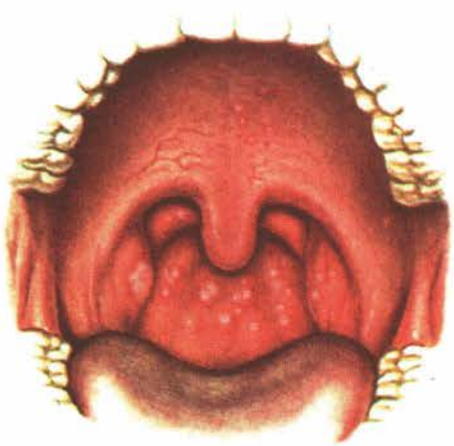
[a] .. = data not recorded.



A

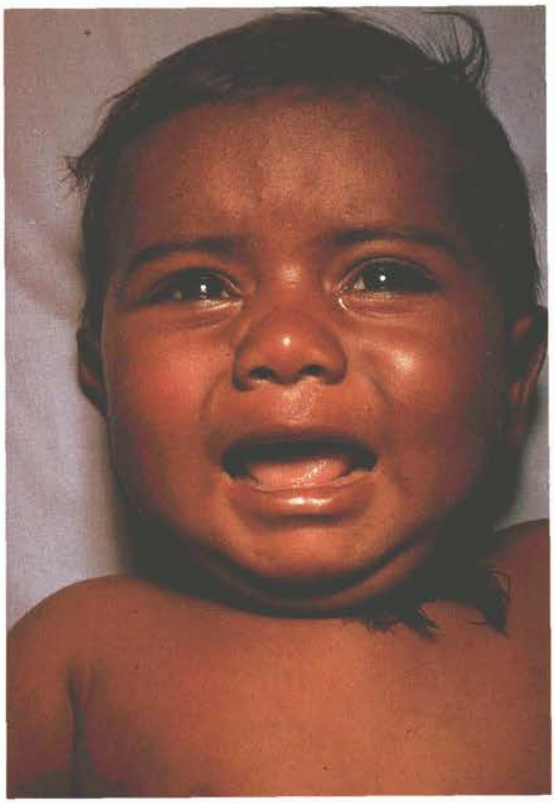
B

Plate 1.3. **A** and **B:** Prodromal rashes. These were best seen in fair-skinned persons (for example, Caucasians and Japanese) and were more common in those previously vaccinated. **A:** Erythematous prodromal rash on the upper arm, near the sites of vaccination performed 8 days earlier but sparing the skin immediately adjacent to the vaccination lesions. **B:** Measles-like prodromal rash on the lateral side of the trunk on the 4th day of illness. **C:** The enanthem. Lesions occurred throughout the oropharynx and in the nasal cavity, as well as on the tongue. The lesions on the palate were usually smaller than those on the posterior pharyngeal wall and tonsil. (From Uchida, 1955.)



C

Day 1



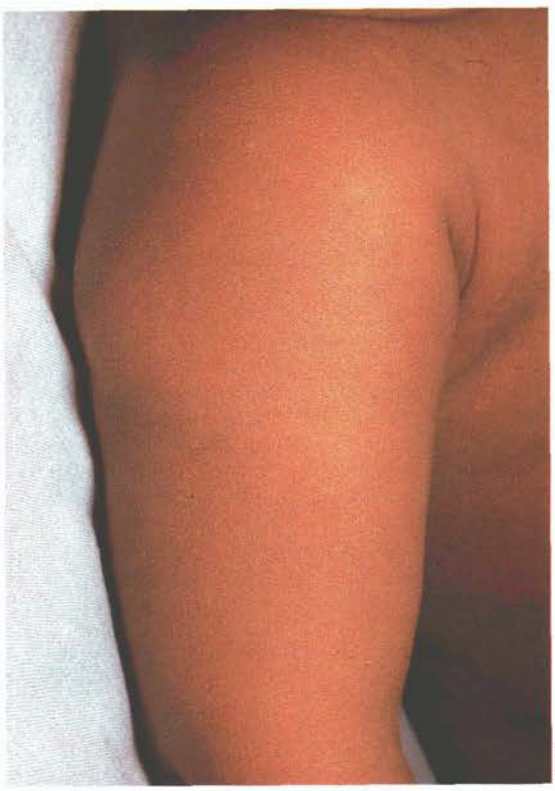
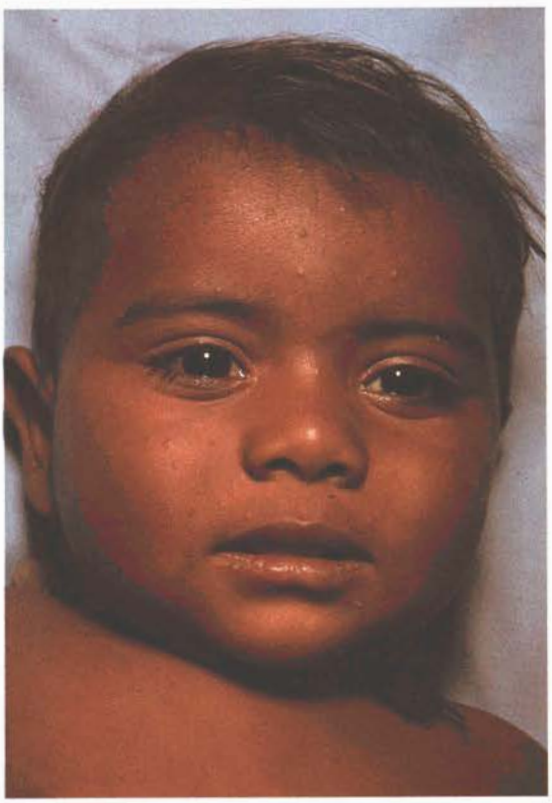


Plate 1.4. This and the next 10 colour plates illustrate the evolution and subsequent healing of the skin lesions in a 9-month-old unvaccinated Pakistani child. The rash appeared 1 day after the onset of fever, and the illustrations are categorized in terms of the day of rash. Each plate shows the ventral surface of the full body, the face, and the upper arm. This plate illustrates the first day of the rash. A few small papules are visible on the face and upper arm. An enanthem would usually have been present in the oropharynx at this time, but cannot be seen in this photograph (see Plate 1.3C).

WHO

Day 2



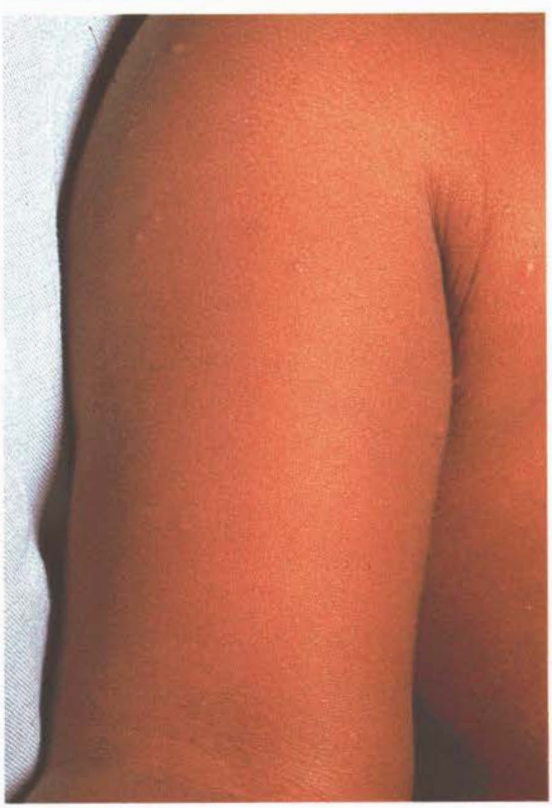
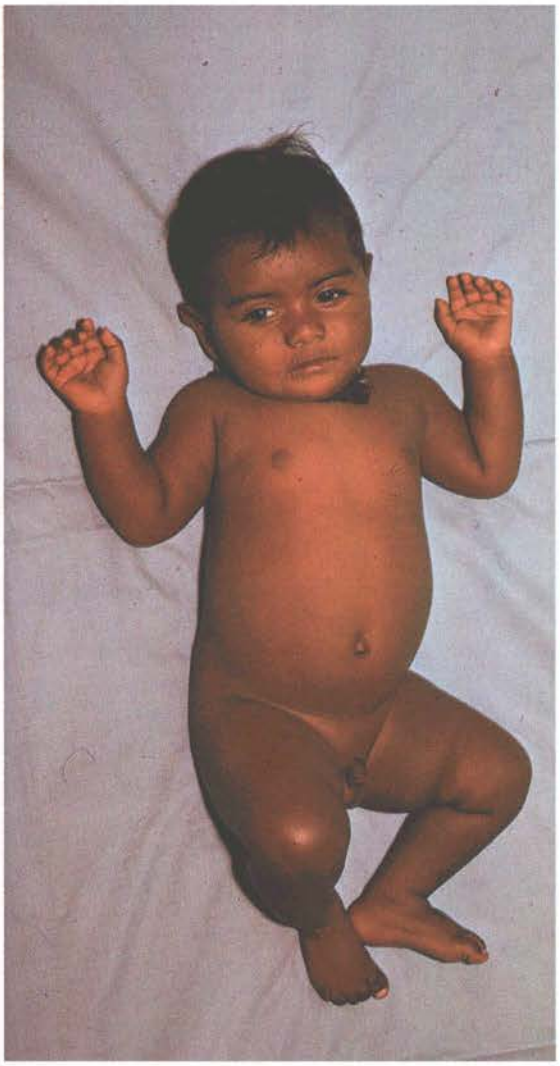
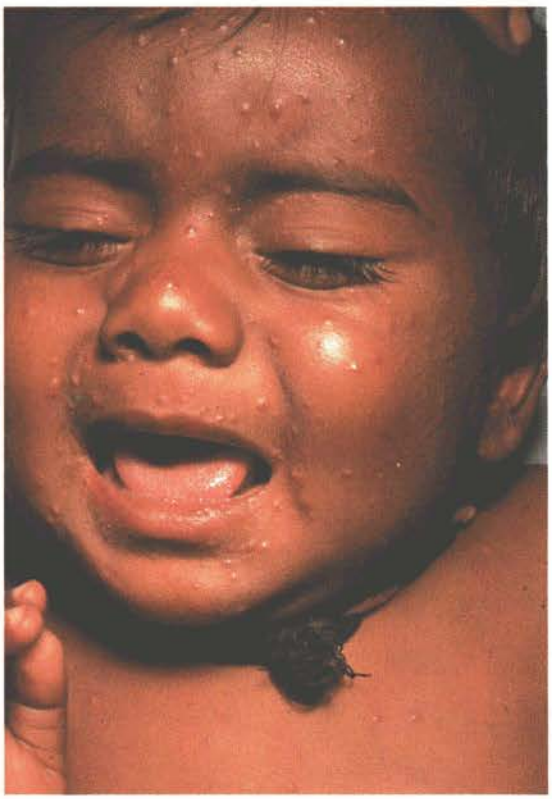


Plate 1.5. Second day of rash. More papules are present, having appeared first on the face and the upper part of the extremities.

WHO

Day 3





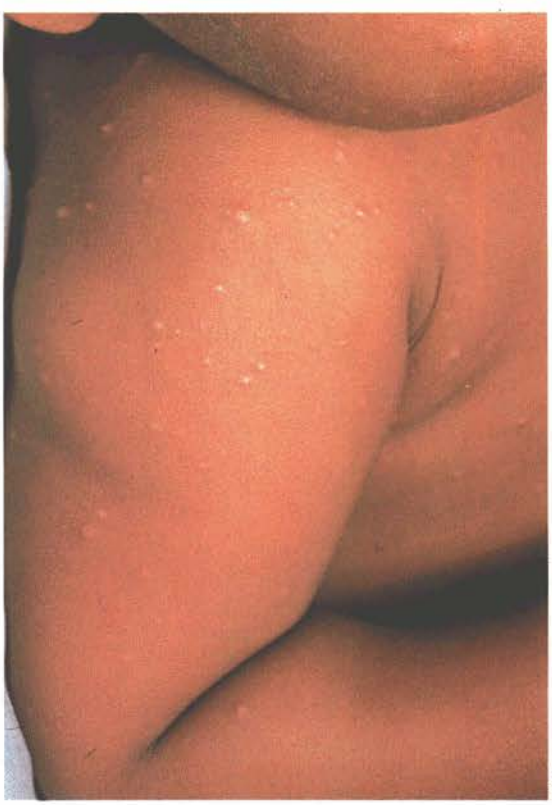


Plate I.6. Third day of rash. Additional lesions continue to appear and some of the papules are becoming obviously vesicular.

WHO

Day 4

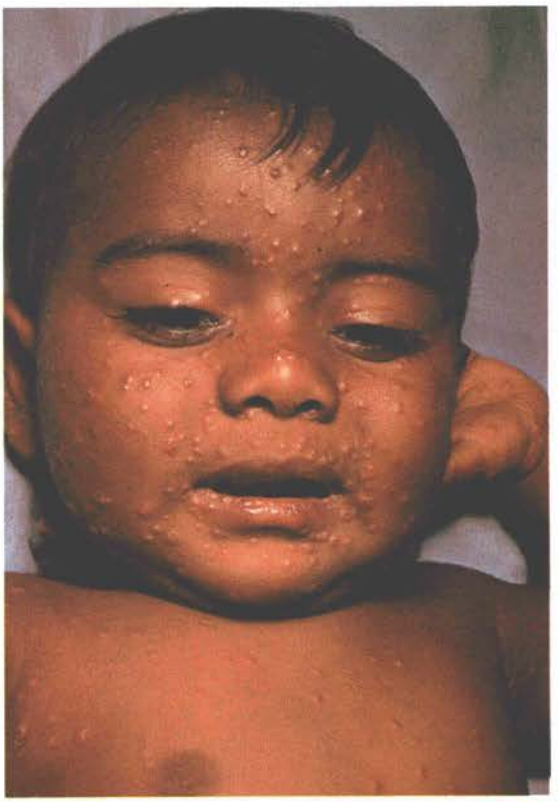


Plate 1.7. Fourth day of rash. All lesions had usually appeared by this time. Those that appeared earliest, on the face and upper extremities, are somewhat more mature than those that appeared later on other parts of the body, but on any specific area of the body all lesions are at approximately the same stage of development. Lesions are present on the palm of the hand.

WHO

Day 5

WHO

Plate 1.8. Fifth day of rash. Almost all the papules have now become vesicular or pustular, the truly "vesicular" stage usually being very brief. Some of the lesions on the upper arm show early umbilication.

Day 6

Plate 1.9. Sixth day of rash. All the vesicles have now become pustules, which feel round and hard to the touch ("shotty"), like a foreign body.

WHO

Day 7

Plate 1.10. Seventh day of rash. Many of the pustules are now umbilicated and all lesions now appear to be at the same stage of development.

WHO

Day 8

Plate 1.11. Eighth day of rash. This case is now clearly classified as discrete ordinary-type smallpox. In the confluent subtype of ordinary-type smallpox the lesions would have been confluent on the face and forearms (see Plate 1.18); in the semiconfluent subtype they would have been confluent on the face but not on the forearms.

WHO

Day 9

Plate 1.12. Ninth day of rash. The pustules have reached their maximum size and are becoming flattened.

WHO

Day 13

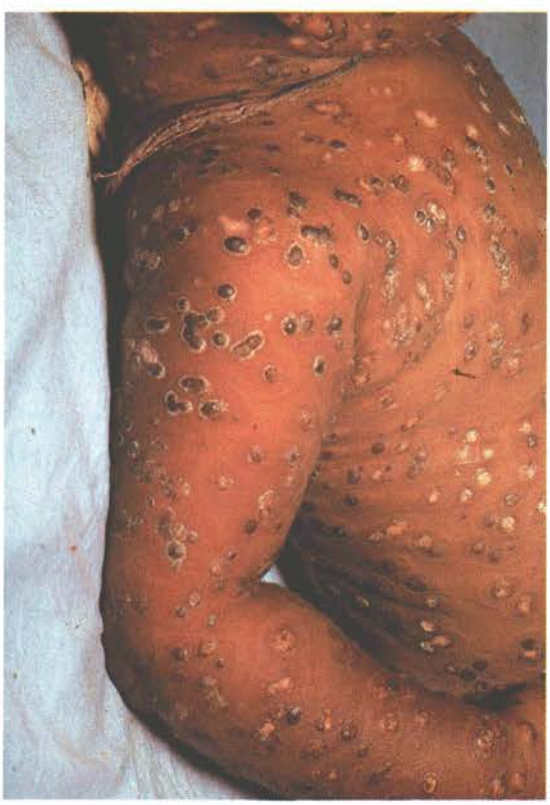
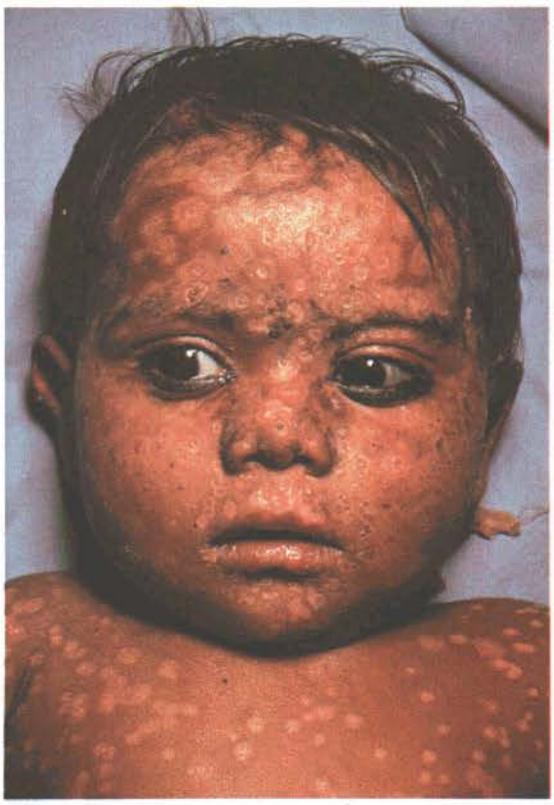


Plate 1.13. Thirteenth day of rash. The lesions are now scabbing, but the eyelids are more swollen than at earlier times. There is no evidence of secondary bacterial infection of the skin lesions.

WHO

Day 20



WHO

Plate 1.14. Twentieth day of rash. The scabs have separated except on the palms of the hands and the soles of the feet, leaving depigmented areas.

The Eruptive Stage

Chapter 3 concludes with an integrated picture of the pathogenesis of smallpox, which was a generalized viral infection with no recognizable primary lesion but with a viraemia whose onset was manifested clinically by the pre-eruptive fever, followed a few days later by the development of a focal eruption on the mucous membranes and skin. Following the example of Ricketts (1908), our description of the clinical features of smallpox is in large part based on illustrations, using a series of colour photographs taken for WHO during the smallpox eradication programme in Pakistan. The subject was a 9-month-old unvaccinated male infant in whom the onset of fever was recorded 1 day before the rash first appeared. He suffered from the commonest form of smallpox—discrete ordinary-type—and recovered without complications. Daily photographs were taken, until recovery was complete, of the entire subject and of face, trunk, arms and legs. Only a limited selection of these can be reproduced here, but they serve to illustrate the nature, evolution and distribution of the rash of smallpox. The temporal succession will be described in terms of the day of rash.

Order of appearance of the focal lesions

The lesions on the mucous membranes (the enanthem—Plate 1.3C) were the first to appear, and they were visible on the tongue and palate, as minute red spots, about 24 hours before the appearance of rash on the skin. Lesions also occurred at this time lower down in the respiratory tract, and some patients, who complained of sore throats during this stage, had an enanthem on the pharynx.

The rash usually appeared between 2 and 4 days after the onset of fever as a few small macules ("herald spots") on the face, especially on the forehead (Plate 1.4). In a few cases the rash was first seen on the forearms or some other part of the body. Lesions then appeared on the proximal portions of the extremities, on the trunk, and lastly on the distal portions of the extremities. However, the lesions appeared in such quick succession that it was difficult to follow the timing of their occurrence on the different parts of the body, and only rarely did a patient notice this order of appearance and give such a history. Usually the rash had appeared on all parts of the body within 24 hours. Additional lesions often appeared during the next one or two days (compare Plates 1.4, 1.5 and 1.6) but normally no fresh lesions appeared after that (Plate 1.7).

In a particular area of the body surface all the lesions were at about the same stage of evolution, although of different sizes, because the rash developed essentially as a single "crop". However, up to the 3rd day, because of the order of their appearance, there were sometimes papules on the face and macules on the legs and similarly, after scabbing had started, lesions might be scabbing on the face and still be pustular on the legs. By the 11th day many of the scabs had come off the face, the temperature had fallen and the patient felt much better. Separation of the scabs proceeded in the same order as the macules and vesicles had appeared, from the face and scalp to the trunk, arms, hands, legs and feet. By the 17th day, only the lesions in the thick-skinned palms of the hands and soles of the feet remained (Plate 1.16).

Evolution and distribution of the enanthem

The enanthem evolved rapidly, because of the absence of a horny layer in the stratified epithelium of the pharynx. The minute macules became papular and vesicular and then broke down before the 3rd day (Plate 1.3C), liberating large quantities of virus into the saliva. By the 10th day they had almost healed.

The visible parts of the oropharynx most likely to show lesions were the hard palate, the tip and edges of the tongue and the pillars of the fauces. Different patients showed remarkable variations in the extent of the enanthem; in cases of equal severity the lesions were sometimes few or absent, or the mouth and throat might have been covered by a confluent enanthem that extended to the larynx and trachea. Although not as spectacular as the rash, the pharyngeal lesions were of great importance epidemiologically, as they constituted the major source from which virus was transmitted to other persons (see Chapter 4).

Evolution of the skin lesions

By the 2nd day of rash the macules were raised and usually described as "papules". Reference to the histopathology indicates that this term was really a misnomer; they were raised above the skin surface because of the effusion of fluid into the tissue spaces and were in fact early vesicles (Plates 1.5 and 1.6).

G. BHAS

Plate 1.15. Section of a skin lesion on the 6th day of rash. Ballooning degeneration of the cells of the lower part of the epidermis has produced a loculated vesicle which is becoming pustular. The keratohyalin and horny layers form the roof of the vesicle; at the base the dermis is undamaged—there will be no scarring after healing. The central depression associated with the hair follicle on the extreme right would produce loculation of the lesion. (Haematoxylin and eosin, x 50.)

By the 4th or 5th day they were obviously vesicular, containing at first an opalescent fluid, which became opaque and turbid in another 24–48 hours (Plates 1.7–1.9).

By the 7th day all the skin lesions were pustules (Plate 1.10) and between then and the 10th day they matured and reached their maximum size (Plates 1.11 and 1.12). By about the 11th day resolution started and the lesions flattened (Plate 1.13). The fluid was slowly absorbed, and by the end of the 2nd week the central portion hardened and finally a scab or crust formed, which later separated, leaving a depigmented area (Plate 1.14).

The palms of the hands and the soles of the feet, because of the very thick stratum corneum, were characterized by the persistence of lesions long after these had scabbed elsewhere. On the soles of the feet especially they had a very characteristic appearance (Plate 1.16). The thick cuticle lay over them and they did not protrude from its level surface, through which the disc-like scabs could be clearly seen. These lesions were called "seeds" and were often artificially removed with a needle in attempts to hasten discharge from the hospital, where patients were usually held until the last scab had separated.

The evolution of the rash can best be appreciated by scanning the series of colour plates provided, which show the lesions daily from the 1st until the 9th day (Plates 1.4–1.12), and then on the 13th (Plate 1.13) and 20th days (Plate 1.14).

Characteristics of the individual lesions

Variolous skin lesions, which usually had only a barely perceptible erythematous areola around them, were traditionally held to have three distinctive characteristics: loculation of the cavity of the vesicle, its umbilication, and the solidity and hardness of the lesion.

Loculation. The reasons for loculation are clear from a consideration of the histopathology (Plate 1.15); it used to be determined in cases of smallpox by piercing the vesicle and observing that the fluid contents could not be completely emptied through the wound. However, this was a rather inefficient clinical

Histopathology of Skin Lesions

In order properly to appreciate the clinical features of the skin lesions it is necessary to consider their histopathology. This is described in detail in Chapter 3, but it is convenient to summarize the main features of the lesions here. Plate 1.15 represents a section of part of a skin lesion in which vesiculation was beginning. The lesion occupied the whole depth of the epidermis, the deeper layers of which provided the floor and the cuticle (stratum spinosum, keratohyalin layer and horny layer) the roof. At the centre the floor was thin and as the lesion grew the deeper layer of basal cells lysed and the dermis then formed the base of the vesicle. But ordinarily (except in the face, where the numerous sebaceous glands complicated the picture) the lesion was contained within the epidermis. As infected cells became necrotic and fluid accumulated, the tissue split, the columns of epidermal cells being forced apart irregularly, so that the fissures were usually perpendicular to the surface and the vesicle consisted of several separate compartments or locules. As cellular necrosis and polymorphonuclear cell infiltration proceeded the fluid became turbid and the lesions pustular, but their turbidity was due to the extensive tissue destruction by the virus and a leukocytic reaction to this; the pus was not associated with bacterial infection.

test, in that it was readily demonstrable in cases in which there was little doubt about the diagnosis but equivocal in cases in which doubt might arise because the vesicles were small or soft. It was rarely used for differential diagnosis by workers engaged in the global smallpox eradication campaign.

The "feel" of the lesion. The skin lesions of smallpox were usually described as "shotty". Although as papules they projected little above the surface, they could be rolled between the thumb and forefinger and felt like hard round foreign bodies embedded in the epidermis.

Umbilication. This term refers to the central depression, of varying size, that was often seen in the distended vesicle. It is well illustrated in Plate 1.8. Umbilication often persisted into the pustular stage, but as the lesion progressed the fibrinous threads within it were destroyed and its surface usually became flattened because of absorption of fluid (Plates 1.11 and 1.12).

Distribution of the rash

The rash of smallpox had a characteristic "centrifugal" distribution pattern. This is apparent in the series of full-body photographs of the Pakistani infant (e.g., Plate 1.11), but is better shown in Plate 1.17. The rash was most dense on the face; more dense on the extremities than on the trunk; and, on the extremities, it was more dense on the distal parts than on the proximal, on the extensor than on the flexor surfaces and on the convexities than on the concavities. The apex of the axilla was relatively free of lesions compared with the folds; this was known as Ricketts' sign. The palms of the hands and the soles of the feet were involved in a majority of cases (Plate 1.16).

On the face, the rash was more profuse on the upper than on the lower half, but in a small proportion of cases it was more uniformly distributed. On the trunk, it was usually denser on the back than on the front, and, on the front, it was more dense on the chest than on the abdomen. On the abdomen, the upper half usually exhibited a more profuse rash than the lower half.

Ricketts (1908) described at length the fine details of the distribution of the rash, which he regarded as a feature of great value in differential diagnosis. Such minute consideration was no longer necessary when laboratory confirmation of a tentative diagnosis became possible. Ricketts also provides several illustrations of the way in which irritation or friction could produce a local concentration of skin lesions. His suggestion that the "centrifugal" distribution of the rash was due to exposure of the face and forearms in habitually clothed persons was not supported by the universal observation of the same characteristic distribution in habitually scantily clothed patients made by workers in several countries during the global smallpox eradication programme.

Clinical Course

The appearance and evolution of the rash in ordinary-type smallpox have already been described and illustrated. In such cases, the fever, which had fallen somewhat on the 2nd or 3rd day after the onset of the disease, when the rash first appeared, usually rose again by the 7th or 8th day and continued to remain high throughout the vesicular and pustular stages, until scabs had formed over all the lesions (see Fig. 1.1).

If secondary pyogenic infection of the skin occurred, the fever usually remained elevated. Respiratory complications, which sometimes developed on about the 8th day of the disease, were either viral or bacterial in origin. In fatal cases, death occurred between the 10th and 16th days of the illness. Among survivors, scabs separated by the 22nd–27th days, but "seeds" in the palms and soles remained much longer unless artificially removed.

Grades of Severity

As has been pointed out earlier, so many cases of variola major belonged to the ordinary type, covering a wide range of severity, that some subdivision that was related to prognosis was found useful. That commonly employed related to the extent of the rash, and the terms "confluent", "semiconfluent" and "discrete" were used by Rao (1972) and others. However, it is important to point out that such grades were part of a continuous spectrum; the numbers of pustules in individual cases could vary from a few to several thousand.

Confluent ordinary-type smallpox

This subtype encompassed cases in which the pustular skin lesions on the extensor surfaces of the extremities as well as those on the face were confluent (Plate 1.18). In such cases the temperature, which had fallen on the 4th or 5th day after the onset, rose again 2 days later and remained elevated until scabbing was complete. Sometimes the toxaemia did not abate and the temperature did not fall even after scabs had formed over all lesions; when this occurred the prognosis was poor. In Rao's series the case-fatality rate of confluent ordinary-type smallpox in unvaccinated subjects was 62%.

Semiconfluent ordinary-type smallpox

This was distinguished from confluent ordinary-type smallpox by an arbitrary criterion: the rash was confluent on the face but discrete on the body, including the forearms. A secondary fever often developed during the pustular stage, but the temperature and toxaemia were less marked than in the confluent subtype and the temperature subsided as soon as the scabbing had started. In Rao's series the case-fatality rate in unvaccinated subjects was 37%.

Discrete ordinary-type smallpox

This was the commonest clinical type in variola major (42% of cases in unvaccinated subjects and 58% of those in vaccinated subjects in Rao's series). Plates 1.11 and 1.17 illustrate such cases. The lesions were fewer in number and discrete (i.e., separated by normal skin) on the face and elsewhere. In some cases, although the lesions were less numerous, the course of the disease was the same as in the other two subtypes; sometimes there was no secondary fever during the pustular stage. The overall case-fatality rate was much lower than in confluent or semiconfluent ordinary-type smallpox—about 9% in unvaccinated subjects in Rao's series.

MODIFIED-TYPE SMALLPOX

In 1908 Ricketts wrote:

"By the use of the terms 'modified smallpox' and 'abortive lesions', no assumption is made as to the state of the patient with regard to vaccination. All that is implied is that he exhibits lesions which, in certain particulars, differ from the type most common among unvaccinated patients. The papules, instead of developing into the large vesicles and pustules of natural smallpox, are transformed into lesions which are generally smaller and often of a different conformation, which do not form pustules of the usual size or wholly fail to suppurate, and which hasten through their course of evolution more quickly than is natural."

This was written before variola minor became endemic in Great Britain. In reviewing data on 13686 cases of variola minor, Marsden (1936) suggested that:

". . . the end results of the action of any of the factors which produce modification are indistinguishable in the individual patient . . . for example, 'variola major' in a vaccinated subject, or in a

Plate 1.16. **A:** Lesions on the sole of the foot on the 14th day of rash. **B** and **C:** Palm of the hand and sole of the foot of a 2-year-old Zairean boy on the 21st day of rash. Elsewhere on the body the scabs had separated; on the palms and soles they remained as dark disc-like scabs ("seeds").

Plate 1.17. Distribution of the rash in smallpox. Dorsal and ventral views of a 3-year-old unvaccinated girl from Zaire, on the 5th day of rash. The case would be classified as mild discrete ordinary-type smallpox. The pustules were characteristically most numerous on the face, arms and legs and rather sparse on the trunk.

Plate 1.18. Confluent ordinary-type smallpox in an unvaccinated woman in her twenties, on the 9th day of the illness. Pustules were confluent on the face, forearms and legs but discrete on the trunk. (From Stojkovic et al., 1974.)

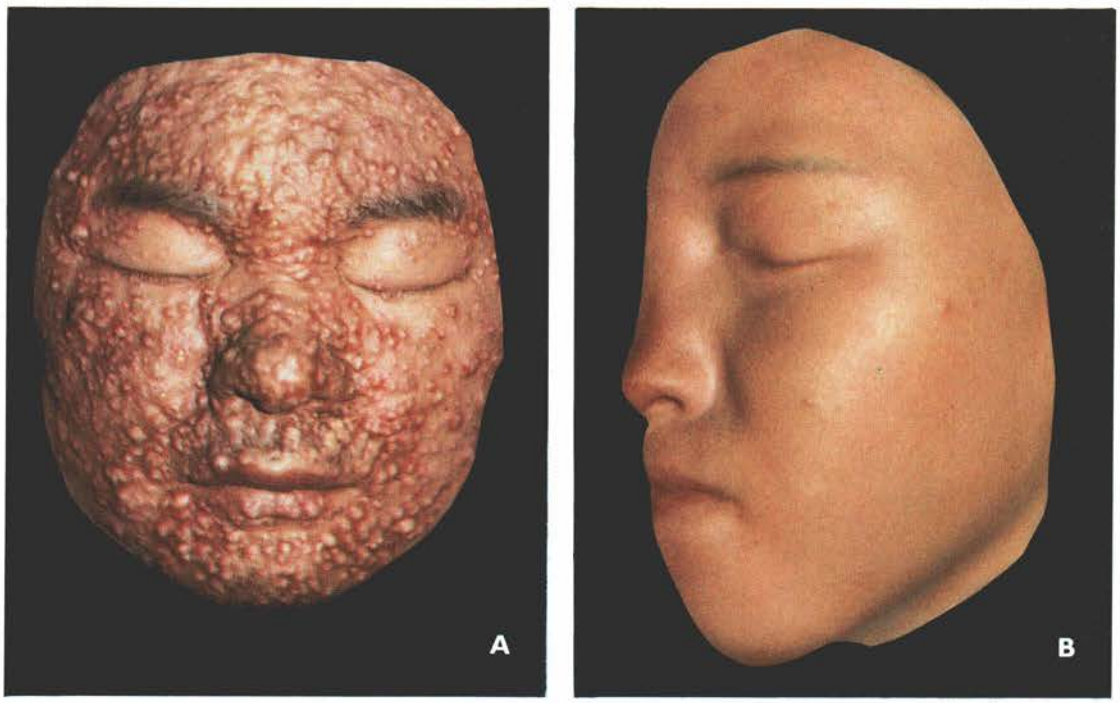


Plate 1.19. Modified-type smallpox. **A:** Vaccinated Japanese man aged 42 years, on the 10th day of the illness. Note the varying size of the lesions and their rapid evolution. **B:** Vaccinated Japanese woman aged 19 years. Very mild case. **C:** Adult female, Delhi, India. Note lack of toxaemia and diversity in size of lesions. (**A** and **B** from Uchida, 1955; **C** from Herrlich et al., 1967.)

Impressions of Smallpox in Bombay in 1958

"The majority of patients had fully developed smallpox in the suppurative stage, with confluent pustules covering the entire body. The head was usually covered by what appeared to be a single pustule; the nose and the lips were glued together. When the tightly filled vesicles burst, the pus soaked through the bedsheet, became smeared on the blanket and formed thick, yellowish scabs and crusts on the skin. When the pulse was taken tags of skin remained stuck to the fingers . . . When secondary haemorrhage appeared, the affected area of skin formed a single black mass.

"All the gravely ill patients were also tortured by mucosal symptoms. The tongue was more or less swollen and misshapen and hindered breathing through the mouth. The voice was hoarse and faltering. Swallowing was so painful that the patients refused all nourishment and, in spite of agonizing thirst, often also refused all fluids. We saw patients with deep invasion of the respiratory passages . . . Wails and groans filled the rooms. The patients were conscious to their last breath.

"Some . . . just lay there, dull and unresponsive. They no longer shook off the flies which sat on purulent eyelids, on the openings of mouth and nose, and in swarms on the inflamed areas of the skin. But they were still alive, and with touching gestures they lifted their hands and begged for help." (Translated from Herrlich, 1958.)

naturally immune, may be indistinguishable at the bedside, as in the laboratory, from 'variola minor'. Furthermore, it is affirmed that the sole method of determining with certainty the primary factor responsible for modification in the individual patient is continued observation of the character of the disease in other patients infected by him or from a source in common with him; and, similarly, that variola major is to be distinguished from variola minor only by epidemiological study of the course of the outbreak; for the clue is to be sought in the fact that, when the infective agent is of a persistently degraded virulence (variola minor), modification of attack is invariable, because it is independent of the patient's immunity."

Following Rao, a WHO Scientific Group on Smallpox Eradication (1968) defined modified-type smallpox in much the same way as had Ricketts:

"In this clinical type, which occurs mostly in vaccinated patients, the modification relates to the character and development of the focal eruption; crusting is complete within 10 days. The pre-eruptive illness may be severe and is not necessarily of short duration, but secondary fever during the evolution of the eruption is usually absent. The skin lesions tend to evolve more quickly, are more superficial, and may not show the uniformity characteristic of the more typical smallpox eruption. The lesions are often few in number, but even when they are numerous they show some pleomorphism and evolve rapidly."

A WHO Expert Committee on Smallpox Eradication (1972) qualified this description by relating modified-type smallpox specifically to smallpox in vaccinated persons.

When preparing this book, we debated this aspect of the definition at some length and eventually agreed to adhere to the older convention—namely, that the term "modified type" connoted smallpox that was accelerated in its clinical course, compared with the expected evolution of ordinary-type variola major, rather than smallpox whose course was modified by vaccination. By far the commonest reason for an accelerated course in variola major was vaccination some years earlier (Plate 1.19), although Mack et al. (1970), who did not categorize any cases as modified-type smallpox, noted that in their series the rapidity of maturation was not associated with either vaccination status or lesion density. In Rao's series, 25% of the cases in vaccinated subjects were classed as modified type, but only 2% of those occurring in unvaccinated subjects were so categorized. No fatal cases occurred in modified-type smallpox. Plate 1.20 illustrates the way in which even confluent lesions could progress much more rapidly than usual. However, modified-type smallpox was usually manifested by fewer lesions as well as by an accelerated clinical course.

VARIOLA SINE ERUPTIONE

Febrile illness sometimes occurred among vaccinated contacts of cases of smallpox, with

Plate 1.20. Confluent modified-type smallpox in a vaccinated adult male. **A**: In the papular stage but profuse. **B**: Early vesicles were confluent and suggested a severe attack, but although the face became swollen (**C**) the lesions did not increase in size and many became prematurely pus-capped. **D**: At a stage when the confluent rash of ordinary-type smallpox would have been approaching its maturity, the lesions had become encrusted and the swelling of the features had subsided. Individual lesions were small, with fleshy deep-seated bases. (From Ricketts, 1908.)

a sudden onset, a temperature of about 39 °C, headache and sometimes backache. Within 48 hours or often less the attack had subsided and the temperature was normal. Without laboratory tests it was impossible to determine whether these symptoms had been due to infection with variola virus, but the finding of high complement-fixing antibody in such patients (see Chapter 3), or a rise in antibody titres between the first and second bleeds, indicated that the fever had indeed been due to infection with variola virus; such cases have been called variola sine eruptione (Table 1.4).

Occasionally viral isolations have been made from oropharyngeal swabs or washings from such patients. Marennikova et al. (1963) mention one such case; virus was recovered

Table 1.4. Serological evidence for variola sine eruptione in contacts of cases of smallpox[a]

Patients' age and sex	History[b]			Antibodies in serum	
	Last vaccination	Contact with smallpox	Serum collection	Neutralization[c]	Complement fixation[d]
20 years (F)	D −1 year (primary)	D −12 days	D −4 days	77%	.
			D +8 days	98%	80
26 years (F)	D −4 years (primary)	D −25 days to D	D +7 days	..	80
33 years (F)	D −33 years (primary)	D −12 days	D +10 days	99%	5
			D +19 days	..	20
Adult, age unknown (M)	D −7 years (revaccinated)	D −12 days	D +10 days	98%	320
33 years (M)	D −4 years (revaccinated)	D −10 days	D +11 days	100%	30

[a] Based on Downie & McCarthy (1958).
[b] D = day of onset of fever; − = time before day D; + = time after day D.
[c] Neutralizing antibodies expressed as percentage reduction of variola virus pock count on the chorioallantoic membrane; .. = data not recorded.
[d] Reciprocal of titre.

Contact Fever

"Variola major was introduced into Durban from India in 1943 and spread widely in South Africa. I was personally involved with one of the patients admitted to Baragwanath Hospital. The physician-in-charge phoned to say that a patient had developed a profuse rash which he felt was probably due to a virus infection. One look at the patient convinced me that she had virulent confluent smallpox. The patient coughed in my face as I was examining her. In spite of having been revaccinated many times, indeed each time I saw a patient with smallpox and again on this occasion and each time responding with an immune reaction, I developed a high fever 12 days later, beginning with chills, muscle pain, especially in the small of the back, and headache and photophobia. My throat became sore and intensely itchy and a white membrane formed on the tonsils and pharynx, presumably an outward sign of an immune reaction taking place at the virus–blood junction. Also of interest was a marked erythematous reaction which developed at the site of the inoculation of the vaccine, presumably an immunological reaction against the antigen deposited at the site in the skin. This reaction became apparent at the time of defervescence. At the same time two vesicles, one on my ankle and one on my wrist, appeared and went through the typical stages of vesicle, pustule and scab.

"My infection seems to have been a case of 'contact fever', a condition which had been recognized as occurring in fully vaccinated individuals many years ago. One of the sisters and the physician attending this patient developed a similar illness also, in spite of revaccination immediately the diagnosis was made." (J. H. S. Gear, personal communication, 1983.)

from pharyngeal swabs obtained on the 3rd day of illness from a patient who did not get a rash. Subsequently, Shelukhina et al. (1973) reported the isolation of variola virus from the throat swab of a recently vaccinated child who had been in close contact with a case of smallpox and who was feverish when the specimen was taken, but who did not develop a rash. Verlinde & Tongeren (1952) reported positive results in 2 out of 13 contacts of cases of variola major from whom pharyngeal washings were taken. One of them was a vaccinated woman from whom virus was recovered on the 14th day after contact, at a time when she had fever and constitutional symptoms. No rash developed. The other person apparently had a subclinical infection (see below).

Sometimes conjunctivitis was the only clinical manifestation of smallpox infection. Dekking et al. (1967) recovered variola virus from the tear fluid of 7 women, all thought to have had smallpox in infancy, who had signs of conjunctivitis after nursing children who died of smallpox. In a study directed at the possibility of conjunctival infection in smallpox contacts, Kempe et al. (1969) reported that conjunctivitis but no other illness developed in 21 out of 55 close family contacts of smallpox patients. Variola virus was recovered from the conjunctival exudate of 12 of them. Four of these 12 patients on whom serological tests were carried out showed antibody rises compatible with recent smallpox.

Medical attendants who had been vaccinated and revaccinated but had not often been exposed to smallpox cases sometimes suffered from what appeared to be an allergic pneumonitis ("smallpox-handler's lung"). Fever, constitutional symptoms and signs of pneumonia developed between 9 and 18 days after exposure to cases of smallpox, and X-rays showed diffuse mottling of the lungs (Howat & Arnott, 1944; Leroux et al., 1955; Evans & Foreman, 1963). None developed a rash, and attempts to recover variola virus from throat washings were unsuccessful.

SUBCLINICAL INFECTION WITH VARIOLA MAJOR VIRUS

There was no easy distinction between variola sine eruptione and subclinical infection, especially among persons living in circumstances in which malaria was endemic and feverish illnesses, from that or other causes, were so common as to be taken for granted.

Evidence from Viral Isolations

Only a few virological studies of smallpox contacts have been carried out (see above and Chapters 3 and 4). Variola virus was occasionally recovered from the throat swabs of such subjects, sometimes for several days in succession, but most of them had been vaccinated and never developed symptoms. Their infections would thus have to be classified as subclinical.

Evidence from Serological Studies

Serological diagnosis of past infection with variola virus depended on the fact that certain serological tests, such as the complement-fixation test, gave positive results (with high titres) for relatively short periods while others remained positive for a prolonged period, both after vaccination and after overt smallpox (Chapter 3).

Heiner et al. (1971a) carried out a detailed study of subclinical infection in villages and individual houses in West Pakistan in 1968–1969, in which overt smallpox had occurred in 68.8% of the unvaccinated and 3.2% of the vaccinated household or compound contacts. Retrospective positive serological diagnoses probably included some cases of smallpox with very few lesions and variola sine eruptione (misdiagnosed or ignored) as well as truly subclinical infections, but the figures obtained give an indication of the frequency of unrecognized smallpox as it occurred in endemic regions.

Two groups of people were studied. "Healthy contacts" were individuals who had not contracted overt smallpox, but had been household or compound contacts of a recent case of smallpox, and had not been vaccinated within 9 months of the study. The principal control group (Group 1 of Table 1.5) consisted of similar subjects who lived in the same villages but had not been in such close contact with smallpox cases. Two subsidiary control groups were used to determine the persistence of antibodies after vaccination; members of one group (Group 2 of Table 1.5) had been vaccinated annually but not within 9 months

Table 1.5. Comparison of titres of complement-fixing and haemagglutinin-inhibiting antibodies among vaccinated close contacts of cases of variola major and vaccinated controls[a]

	Number of close contacts	Number of controls[b]		
		Group 1	Group 2	Group 3
	143	62	37	40
Complement fixation:				
Geometric mean	38.6	<10	<10	<10
% of sera ≥ 1/40	54.5	6.5	8.1	10.0
Haemagglutination inhibition:				
Geometric mean	10.5	<4	4.2	5.8
% of sera ≥ 1/16	49.0	11.3	13.5	22.5

[a] Based on Heiner et al. (1971a).
[b] Group 1: village contacts; Group 2: vaccinated annually; Group 3: vaccinated 5 years or more before study.

of the study, and members of the other group (Group 3 of Table 1.5) had last been vaccinated 5 years or more before the study. The highly significant differences between the close contacts and controls revealed by these tests were supported by similar results using other serological tests (neutralization, passive haemagglutination-inhibition and immunodiffusion). The frequency distribution of positive titres among the controls was unimodal, the majority being negative or having very low titres (Fig. 1.2). The titres of the contact group had a bimodal distribution, about half being negative or very low and the other half positive. This serological evidence indicates that subclinical infection that was accompanied by enough replication of virus to stimulate the production of complement-fixing and haemagglutinin-inhibiting antibodies occurred in many of the vaccinated close contacts of cases of variola major. Rao et al. (1970) came to a similar conclusion, using a gel-precipitation test with both variola and vaccinia antigens. There was also suggestive but inconclusive evidence that inapparent infection occurred among subjects who had recovered from smallpox years before, a result that has parallels in measles (Ueda et al., 1969).

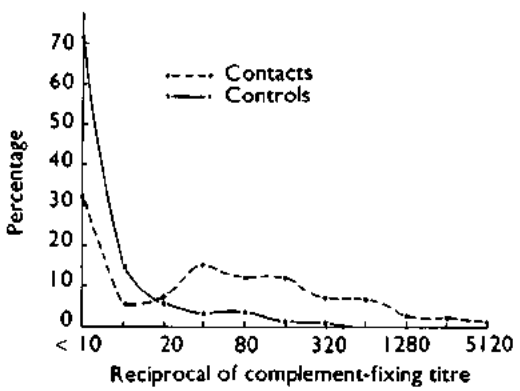


Fig. 1.2. Distribution of titres of complement-fixing antibodies to variola antigens in contacts and controls, as defined in text. (Data from Heiner et al., 1971a.)

FLAT-TYPE SMALLPOX

Flat-type smallpox was so called because the lesions remained more or less flush with the skin at the time when raised vesicles formed in ordinary-type smallpox (Plate 1.21). This manifestation of the disease was seldom encountered (6.7% of cases in unvaccinated subjects in Rao's series), and the majority of cases (72%) occurred in children. It was very rare in successfully vaccinated subjects. The prognosis was always grave and most cases were fatal (see Table 1.2).

The pre-eruptive stage lasted 3–4 days, with the usual constitutional symptoms, which were severe and continued after the appearance of the rash. The fever remained elevated throughout and the patient had severe toxaemic symptoms.

The Rash

The enanthem on the tongue and palate was usually extensive and sometimes confluent. Occasionally a severe enanthem occurred on the rectal mucous membrane. The characteristic feature of flat-type smallpox was the nature of the skin lesions. Unlike the regular evolution seen in ordinary-type smallpox, the focal lesions in the skin matured very slowly, and at the papulovesicular stage, about 6 days after the onset of fever, a small depression was visible. By the 7th or 8th day the lesions were flat and appeared to be buried in the skin (Plate 1.21). Most lesions had haemorrhages

into their base, the central flattened portions appeared black or dark purple, and they were surrounded by an erythematous areola. The lesions differed from those of ordinary-type smallpox in that the vesicles contained very little fluid, they were not multilocular, and they did not show umbilication. In contrast to the "shotty" feel of the lesions in ordinary-type smallpox, they were soft and velvety to the touch. No further evolution of the lesions occurred and frank pustules were rarely seen, although occasionally a few lesions, especially on the dorsum of the feet and hands, became pustular, while elsewhere on the body they remained as flat vesicles. Because of their superficial nature, the skin over the lesions peeled off after slight trauma, sometimes leaving extensive raw areas. Often the skin lesions did not conform to the classical "centrifugal" distribution.

Clinical Course

Throughout the course of the disease the patient was toxic and febrile. Respiratory complications, including oedema of the lung and sometimes frank pneumonia, set in by the 7th or the 8th day after the onset of fever. Rao noted that unvaccinated children sometimes developed an acute dilatation of the stomach 24–48 hours before death, which usually occurred between the 8th and the 12th day. A day or two before death, the colour of the lesions changed to an ashen grey, which, along with acute dilatation of the stomach, was a bad prognostic sign. In cases with a confluent enanthem on the tongue and palate, the mucous membrane sloughed, leaving large raw areas. Some patients passed blood and mucus in the early stages of the disease, indicating the extensive involvement of the rectal mucous membrane, and in such cases, just before death, the rectal mucous membrane was sometimes sloughed off.

Among the few who survived, scabbing usually began on about the 13th–16th day after the onset of fever and was complete by about the 21st day. The scabs were thin and superficial and separated rapidly, leaving very superficial scars. Because of the bleeding into the base of the lesions, the scabs, before they dried, were purplish in colour.

Flat-type smallpox was probably due to the infection of particularly susceptible subjects with virulent strains of variola virus; it never occurred in variola minor. The appearance of the lesions suggested a deficient cellular immune response in these patients, but no relevant studies were ever reported.

HAEMORRHAGIC-TYPE SMALLPOX

General Features

Considering its comparative rarity (only 200 cases in Rao's series of 6942 hospitalized patients in Madras), a great deal has been written about haemorrhagic-type smallpox. No doubt this preoccupation was partly due to the rarity of the syndrome, its great severity and the difficult problem that it presented in differential diagnosis. This was particularly true in countries in which smallpox was no longer endemic; there were many instances in which outbreaks or their extension could be traced to an unrecognized importation of haemorrhagic-type smallpox (see, for example, Benn, 1963; Stojkovic et al., 1974).

Histopathological studies (Bras, 1952a) support the clinical distinction of two varieties of haemorrhagic-type smallpox—what Curschmann (1875) and Immermann (1895) called "purpura variolosa" and "variola pustulosa haemorrhagica." We shall follow Rao (1972) in calling them early and late haemorrhagic-type smallpox respectively. Early haemorrhagic-type smallpox was characterized by haemorrhages into the skin and/or mucous membranes early in the course of the illness. Subconjunctival haemorrhages were the most common, and bleeding from the gums, epistaxis, haematemesis, haemoptysis, haematuria, as well as vaginal bleeding in women, occurred at any time in the course of the illness.

In late haemorrhagic-type smallpox haemorrhages into the skin and mucous membranes often occurred, and usually also into the bases of the developing skin lesions. Some of these cases could equally well have been considered as cases of flat-type or confluent ordinary-type smallpox, associated with haemorrhages as a complication. However, all classifications contain an arbitrary element.

Haemorrhagic-type smallpox, of both subtypes, had two unusual epidemiological features: it occurred mostly in adults (Calcutta: Guha Mazumder et al., 1975; Madras: Rao, 1972) and in some extensive series (the Calcutta and Madras series) it was as common in vaccinated as in unvaccinated subjects (see

Plate 1.21. Flat-type smallpox. **A:** Adult Indian man. **B** and **C:** Unvaccinated young woman from Madras, India, on the 6th day of rash; she died 3 days later. Note severe toxaemia and extensive flat pustules in both cases. (**A** from Herrlich et al., 1967.)

Plate 1.22. Early haemorrhagic-type smallpox. **A:** In an unvaccinated 60-year-old woman, who died on the 4th day of illness. Besides the rash illustrated she bled from many other sites, with subconjunctival haemorrhages, a bloody enanthem, epistaxis, haematuria, blood in the faeces and metrorrhagia. **B:** Subconjunctival haemorrhage. **C:** Fully developed haemorrhagic diathesis and death. (**A** from Stojkovic et al., 1974: **B** and **C** from Herrlich et al., 1967.)

Plate 1.23. Contrast between early and late haemorrhagic-type smallpox. **A** and **B:** Early haemorrhagic-type smallpox in a pregnant 18-year-old woman, showing severe toxaemia, petechial exanthem and bleeding from body openings; 1 hour before death. **C:** Late haemorrhagic-type smallpox in young woman, showing bleeding in base of pustules and development of a general haemorrhagic diathesis late in the disease. (From Herrlich et al., 1967.)

I. ARITA

Plate I.24. Variola minor in a 30-year-old unvaccinated Somali woman, 12 days after the onset of rash. The patient was not very sick and was ambulant throughout the disease. The lesions on the face were sparse (**A**) and evolved more rapidly than those on the arms and legs (**B** and **C**).

Table 1.2). On the other hand, Sarkar et al. (1972), in a series of 170 cases observed in Calcutta during the years 1963–1969, recorded no cases of haemorrhagic-type smallpox among 81 patients who had been vaccinated but did note 32 cases among 89 unvaccinated subjects.

Early Haemorrhagic-Type Smallpox

With minor changes, descriptions of early and late haemorrhagic-type smallpox, and statistical data relating to them, are taken from Rao (1972). There is no point in trying to distinguish a "pre-eruptive" stage in this subtype, since death usually occurred before the focal rash had time to develop. The onset was sudden and the high fever was accompanied by severe headache and backache which often persisted until the patient died. Patients looked very sick and were restless, anxious and pale. On the 2nd day of fever the whole body was suffused with a generalized erythema, and petechiae and areas of ecchymosis appeared (Plate 1.22A and C). Subconjunctival haemorrhage was the most common (Plate 1.22B), but haemorrhages occurred from many sites (Table 1.6). On the 3rd day of the disease, the whole skin exhibited a finely textured matted surface and was velvety to the touch (Plate 1.23A and B), and 24 hours later it resembled dark-purple velvet, a feature seen most clearly in fair-skinned patients.

Patients showed signs of severe toxaemia, and became restless, breathless, and complained of heaviness and pain in the chest. Ricketts (1908) described and illustrated a characteristic expression of the face, with the features immobile, the lines of expression obliterated, the cheeks relaxed, the lips full and parted and the eyelids drooping—an expression of profound prostration. He also spoke of a fetid odour of the breath that was common to the toxaemic state in most cases of very severe smallpox, whether they were haemorrhagic, flat or confluent ordinary in type. Death occurred rather suddenly on about the 6th day of fever, patients usually remaining conscious until the end. Clinical observation and postmortem studies (Bras, 1952a) revealed that these patients did not die of haemorrhage, but they showed evidence of heart failure and sometimes oedema of the lungs. If the patient survived a few days longer, the superficial layers of the skin became raised and fluid collected underneath, forming large blebs containing serous or serosanguinous fluid, which ruptured after slight trauma, leaving extensive raw areas.

As was true for haemorrhagic-type smallpox in general, the early haemorrhagic subtype was more common in adults, 88% of all cases in Rao's series being in persons over 14 years of age. Two-thirds of his cases were in women, pregnant women being especially susceptible. Of all the smallpox cases occurring in pregnant women in the Madras series, 16% were of this subtype, compared with only 0.9% among non-pregnant females and 0.8% among males in the age group 15–44 years. If a vaccinated person contracted haemorrhagic-type smallpox the outcome was not influenced by the prior vaccination; indeed, Rao (1972) states that a few cases of fatal early haemorrhagic-type smallpox occurred even among persons who had recently been successfully revaccinated.

Table 1.6. Frequency of haemorrhages (percentages of cases) in different anatomical sites in early and late haemorrhagic-type smallpox[a]

Site or symptom	Early haemorrhagic type (72 cases)	Late haemorrhagic type (128 cases)
Skin	85	16
Conjunctiva	65	52
Haematuria	25	29
Gums	20	29
Haemoptysis	12	30
Melaena	10	8
Epistaxis	2	3
Haematemesis	1	4
Vagina (women only)	80	58

[a] Based on Rao (1972).

Late Haemorrhagic-Type Smallpox

This form was differentiated from early haemorrhagic-type smallpox by the occurrence of haemorrhages after the appearance of the rash. The pre-eruptive stage lasted for 3–4 days, the temperature being about 40 °C, with severe toxaemic symptoms like those described for early haemorrhagic-type smallpox, which continued unabated even after the appearance of the rash. The lesions, which started as macules, soon became papules but thereafter matured very slowly. They sometimes showed haemorrhages into their bases, which gave them a "flat" appearance (Plate 1.23C). Bras (1952a) noted that sections of such lesions showed that often the bleeding actually occurred in the corium beneath the pustules rather than in the pustules themselves.

Bleeding occurred in various mucous membranes, although somewhat less frequently than in early haemorrhagic-type smallpox (Table 1.6). If the haemorrhagic focal lesions were "flat", they did not evolve beyond the vesicular stage but then flattened out and became black. In about 15% of Rao's cases they matured into pustules, which followed the same course as in ordinary-type smallpox. In these cases there were no haemorrhages into the lesions, but only into mucous membranes.

The majority of cases of late haemorrhagic-type smallpox were fatal (see Table 1.2), death occurring between the 8th and the 10th day. Cases with flat lesions had a higher fatality rate than those with raised pustular lesions. Among the patients who survived, the haemorrhages gradually resolved during a prolonged convalescence. However, in the few survivors among cases with the flat type of lesions, scabs usually formed sooner, resulting in only superficial scarring.

Of cases in the Madras series, 80% occurred in persons over 14 years old. Unlike the situation with early haemorrhagic-type smallpox, there was little difference in frequency between men and women, although pregnant women were slightly more susceptible. In Rao's series, of all pregnant women with smallpox, 6% had the late haemorrhagic type, compared with 2% of non-pregnant females and 2.1% of males in the age group 15–44 years. As with early haemorrhagic-type smallpox, Rao observed cases among persons who had apparently been successfully vaccinated, not only in infancy but also at later ages.

Haemorrhagic-type smallpox was primarily due to defects in the response to infection by individual patients. It was very rare in variola minor (see below), but epidemiological evidence suggested that viral strains of unusual virulence were not the main cause of haemorrhagic-type smallpox. For example, Rao (1972) noted that there had not been a single haemorrhagic-type case among the contacts of 385 cases of haemorrhagic-type smallpox in Madras, although many of these contacts had contracted other forms of smallpox; this was an even longer series than that analysed in Table 1.2. Postmortem studies (Bras, 1952a) excluded concomitant bacterial infection as a precipitating factor. As will be shown in a later section, these cases were characterized by high and sustained viraemia, severe depletion of platelets and a poorly developed humoral immune response.

VARIOLA MINOR

This variety of smallpox differed greatly from variola major in its spectrum of severity and in its case-fatality rates—about 1% compared with about 20%.

Clinical Course

The most comprehensive account of the symptomatology of this disease was provided by Marsden (1936). His observations were based on 13686 cases (most of which he examined personally) that occurred in London between 1928 and 1934. The description which follows is drawn largely from that source, supplemented by the accounts of MacCallum & Moody (1921), Jong (1956) and Noble et al. (1970), and the extensive field experience of epidemiologists working in Brazil, Ethiopia and Somalia during the smallpox eradication programmes in those countries.

Almost all cases of variola minor would have been classified as discrete ordinary- or modified-type smallpox, but in any individual case it was impossible to determine whether the disease was variola major or variola minor. The diagnosis depended on the assessment of the clinical severity of the outbreak; if there were no deaths or only one among 50 or so patients the disease was usually variola minor. Data on the pre-eruptive stage were provided by Marsden, who saw only about 1% of his cases at this stage, and MacCallum & Moody

JOYCE GREEN HOSPITAL, DARTFORD, ENGLAND

Plate 1.25. James Pickford Marsden (1900-1977). Formerly Deputy Medical Superintendent, River Hospitals (London County Council), Dartford, Kent, England. He described a series of 13 686 cases of variola minor in outbreaks in London between 1928 and 1934.

(1921), who saw many of the 2333 cases in their Jamaican series during the early stages of the disease. The onset was sudden, with a fever of 40 °C, severe headache and backache and sometimes vomiting. Marsden recorded the occurrence of pre-eruptive rashes in 48 of the cases he saw during this stage; there were typical erythematous prodromal rashes in 37 cases. MacCallum & Moody recorded no such rashes in their mainly dark-skinned patients. The constitutional symptoms of the established disease were usually much less severe than those in cases of variola major with a comparable rash (Plate 1.24). The toxaemia so evident in variola major rarely occurred, and patients with extensive skin rashes were often ambulant. The individual lesions were smaller than those of variola major, so that Marsden was able to count more than 500 lesions on the faces of 295 of his patients without these producing confluence, as would have been expected in variola major. Both MacCallum & Moody and Jong noted that the early vesicles and early pustules were unilocular and were not umbilicated, a clinical finding that was supported by histological examination of biopsy material. The sequence of appearance, the distribution and the nature of the skin lesions were similar to those described earlier for variola major, but their evolution was often more rapid. The eruption became vesicular on the 3rd day after the appearance of the first papules, and within 24 hours had become pustular. Early crusting was established on the 6th or 7th day of rash.

Cases of variola minor could not be classified according to Rao's scheme (see Table 1.1) because of the smaller size and more rapid evolution of the skin lesions. Indeed, the vast majority would have been classified as "modified-type smallpox", which would clearly be a misnomer. Marsden grouped his cases according to the criteria formulated by Ricketts (1893) (Table 1.7). He noted that many of those classified as "discrete" would have been confluent in variola major; none was described as flat-type smallpox.

In keeping with the reduced severity and the more rapid evolution of the rash, secondary fever was rare, occurring in most of the more severe cases but, in Marsden's experience, in only 0.13% of those with fewer than 100 lesions on the face, a group which included 87% of the cases in his series. Both MacCallum & Moody and Jong noted the absence in variola minor of the characteristic fetid odour of variola major.

Haemorrhagic-type cases did occur in variola minor, but they were extremely rare. Marsden recorded 3 cases, one of which recovered; Tigre et al. (1973) describe a fatal case in a 4-year-old boy infected in Argentina in 1970 and refer to 4 others observed in Brazil; Rodrigues-da-Silva et al. (1963) recorded 1 case which survived, and Moody (1922) recorded 2 fatal cases, both in pregnant

Table 1.7. Classification of clinical type of cases of variola minor[a]

	Number	Percentage
Haemorrhagic or toxic	3	0.02
Confluent on face	19	0.13
Discrete; >500 pocks on face	295	2.16
Discrete; 100–500 pocks on face	1 484	10.84
Discrete; < 100 pocks on face	11 885	86.85

[a] Based on Marsden (1936).

women, among 2912 cases of variola minor in an epidemic in Jamaica in 1920–1921.

There were 150 pregnant women in Marsden's series but he commented only on the effects on the fetus, described below, and not on the severity of disease in the mother. The mortality in the Jamaica outbreak described by MacCallum & Moody (1921) was 0.4%, but of the 5 women who died 4 were 6 or 7 months pregnant and all of them displayed a "marked tendency to haemorrhage".

Variola Sine Eruptione and Subclinical Infection

In a susceptible population the host resistance to any infection has a Gaussian distribution. The data on variola major (see Table 1.2) suggest that there would be few cases of variola sine eruptione and subclinical infection in unvaccinated persons exposed to this infection; however, many more such cases might be expected to occur in variola minor (Table 1.7). Data on the occurrence of such infections are difficult to find, but observations made in Brazil during the 1960s support this view. Positive titres of complement-fixing antibody were found in 6 asymptomatic contacts of children with overt variola minor; most of the contacts had not been vaccinated more recently than 20 years before (Rodrigues-da-Silva et al., 1963). In a carefully studied ward outbreak, Salles-Gomes et al. (1965) observed positive complement-fixing and sometimes haemagglutinin-inhibiting antibody responses among 13 contacts exposed to overt variola minor. Four of these cases occurred in previously fully susceptible patients who had never had variola or been vaccinated.

SMALLPOX ACQUIRED BY UNUSUAL ROUTES OF INFECTION

Inoculation Variola and Variolation

Under unusual conditions, smallpox could be accidentally acquired through inoculation. Such cases sometimes occurred among nursing mothers and among those engaged in postmortem work (Lyons & Dixon, 1953), and cutaneous infections were recorded in an outbreak among lace-workers (Boobbyer, 1894). Marsden (1936) recorded 50 cases of accidental smallpox inoculation in variola minor and noted that the lesions of inoculation were usually recognized by their larger size and more advanced development than the other elements of the focal rash.

Much more common, however, was the practice of deliberately inoculating variola virus into the skin, practised since ancient times in Africa and India and in China (where, however, infection was usually produced by nasal insufflation) and on a large scale in some parts of Europe and North America during the 18th century (see Chapter 6). Variolation continued to be practised in many parts of Africa and in Afghanistan and Pakistan until quite recent times, and the spread from variolated individuals was an important source of smallpox in Afghanistan and Ethiopia up to the time of eradication in 1973 and 1976 respectively.

The technique of cutaneous variolation has varied at different times and in different places. Detailed descriptions of the methods used during the 18th century in France and other countries of Europe and in North America can be found in Miller (1957) and Razzell (1977b); methods used more recently in Africa and Asia are described in Chapters 14 and 21.

Clinical picture

The clinical picture of inoculation smallpox was influenced by several factors. Inoculation carried out after the manner of modern vaccination produced a local skin lesion that first appeared as a small papule on the 3rd day after the operation. It grew in size and became vesicular by the 5th day, and by the 8th or 9th day there was a large pustular lesion with much surrounding erythema and oedema (see Chapter 6, Plates 6.1–6.3). Fever and constitutional symptoms corresponding to the pre-eruptive stage of ordinary-type smallpox began on the 8th day and often lasted for only 2 or 3 days (Fig. 1.3). There were usually a number of secondary lesions around the primary lesion (see Plates 6.1–6.3), and the generalized rash began on the 9th day on the face, often consisting of very scanty macules, which rapidly became vesicular. Subsequent lesions sometimes appeared over the next 3 or 4 days and evolved more rapidly than in smallpox acquired by the respiratory route. Even in the few cases that had a large number of secondary pustules (which in inoculation smallpox amounted to as many as 300–1000), the lesions matured more rapidly than in

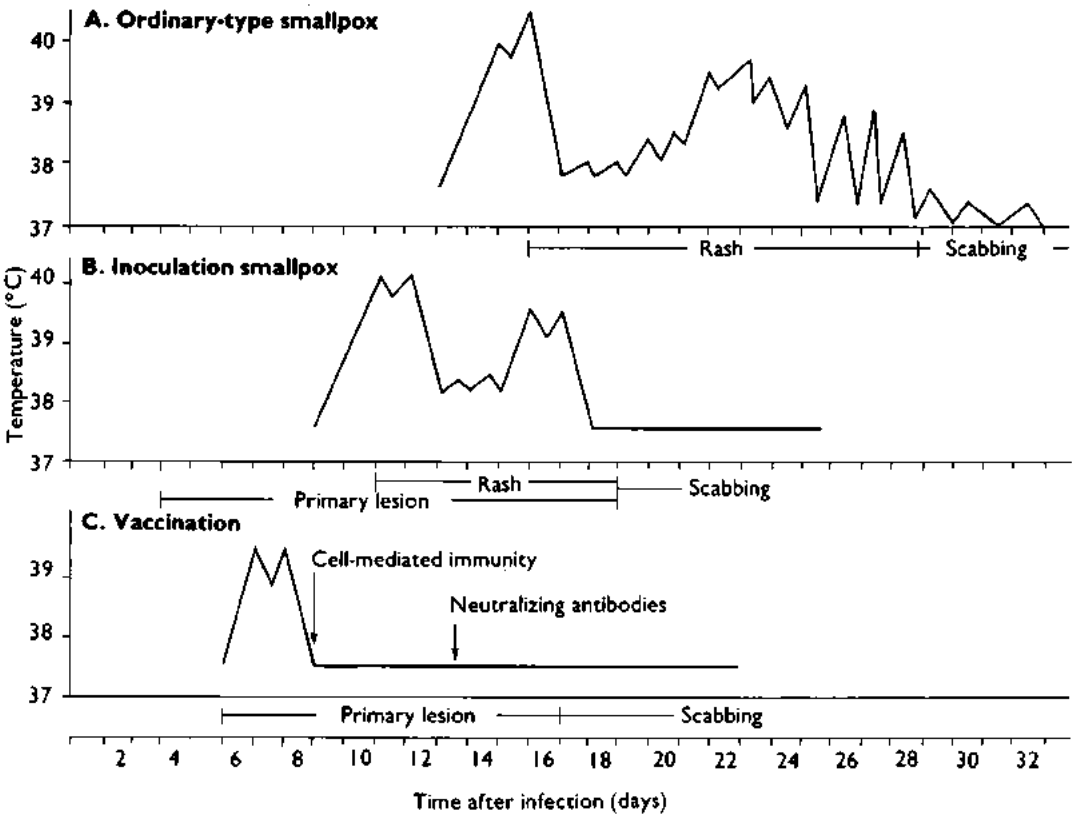


Fig. 1.3. The clinical course of moderately severe ordinary-type variola major in an unvaccinated subject (A); inoculation smallpox (variolation) in an unvaccinated subject (B); and primary vaccination (C). (Temperature records from an illustration in Hime (1896) with modified wording.)

ordinary-type smallpox, so that scabbing occurred 3 or 4 days earlier and the lesions, being more superficial, gave rise to less scarring. By the 18th or 19th day most of the scabs, except for the lesions on the palms of the hands and the soles of the feet, had been shed.

Neither haemorrhagic- nor flat-type smallpox seems to have been recorded as a sequel to variolation, at least in European and North American practice. This may have been due to the professional interests of the inoculators and their concern to be exempt from any possible blame for deaths that occurred; but, in any event, it was the practice to avoid inoculating especially susceptible persons—pregnant women, children under 2 years of age and the aged and infirm.

Apart from the primary skin lesion, most cases, like those of naturally acquired inoculation smallpox, appeared to fall into the category of modified-type smallpox. Cases with only a primary skin lesion, 1 or 2 days of fever and no rash –variola sine eruptione were said to be not uncommon. Rao himself suffered from such an infection (Rao, 1972).

Because of the smaller number of lesions and their more rapid maturation, cases of inoculation smallpox were less infectious, and were infectious for shorter periods, than those of smallpox acquired by the respiratory route. Nevertheless, they often did initiate smallpox in unvaccinated (and unvariolated) contacts, both in 18th century practice in Europe and North America and in recent times in Afghanistan and Ethiopia. Such contact cases were no different from those associated with other epidemics due to whatever strain happened to have been used for variolation.

Severity

In the hands of some of the famous British practitioners of variolation (e.g., the Suttons—see Razzell, 1977b) the severity of smallpox due to variolation appears to have been low and the mortality less than 2%.

In their day only variola major virus was circulating in Great Britain and some contact cases acquired severe and sometimes fatal smallpox; the explanation for the mild nature of smallpox after variolation lay with the age and health of the inoculated subjects, the route of inoculation and the small dose usually employed.

In Ethiopia, where variolation was practised until 1976, the virus used during the last few decades was variola minor and inoculation smallpox was correspondingly mild; nevertheless, it was an important source of outbreaks during the latter part of the eradication campaign in that country (see Chapter 21).

Congenital Smallpox

The effects of pregnancy on the clinical course of smallpox in the mother are discussed later in this chapter. Infection of the fetus depended on the growth of the virus in the placenta and its subsequent release into the cord blood. Its frequency was uncertain, since most pregnant women suffering from variola major aborted during the pre-eruptive fever. Occasionally babies born of mothers suffering from smallpox developed symptoms after birth; Rao (1972) records 10 such cases among 116 live births. In these babies, all of whom died, the fever-to-fever interval was 9–12 days. Among the offspring of 84 women who suffered from haemorrhagic-type smallpox (all with intense and sustained viraemia) none of the 21 children born alive developed clinically recognizable congenital smallpox, but 17 of them died in less than 72 hours—too soon for a diagnosis to be made.

The baby was infected in half of 34 pregnancies in which the mother was infected with variola minor during late pregnancy (Marsden & Greenfield, 1934). Usually the infection was acquired *in utero*, at the time of the mother's viraemia; the incubation period then appeared to be 8–9 days, as in inoculation smallpox. If the fetus escaped infection during that time the infant might become infected at birth or later in the neonatal period, especially if the mother's rash was then at an early stage of development. If the mother carried the fetus to term, the newborn infant was usually temporarily immune from smallpox because of maternal antibodies.

Fetal variola was a rare occurrence, reported only in variola minor. In some cases (MacCallum & Moody, 1921; Ribeiro et al., 1965) the fetus sustained an attack of smallpox *in utero* and was subsequently born alive, having been infected at the time the mother had the disease 2 or 3 months before birth. More often (for example in 8 of the 20 pregnant women in the series described by MacCallum & Moody (1921)) abortion occurred and the macerated fetus was marked with scars from an attack of variola minor sustained *in utero*.

Nowhere in the scientific literature is there a reliable reference to the occurrence of congenital defects caused by smallpox or vaccination in a pregnant woman. Since the usual viral causes of congenital defects are non-cytocidal viruses, whereas variola and vaccinia viruses are both cytocidal, this is not unexpected.

EFFECTS OF VACCINATION ON THE CLINICAL COURSE OF SMALLPOX

The most important effect of vaccination was the protection of the subject from smallpox, but prior vaccination, even many years before, usually influenced the course of the disease in persons who did show symptoms. The situation in individual subjects depended on a variety of factors, some relating to the host: genetic resistance, physiological state, and interval since vaccination or revaccination; some to the vaccine and its mode of delivery: the strain of vaccinia virus used, the potency of the vaccine and the inoculation procedure employed; and, finally, of course, whether the infection was due to variola major or variola minor virus. Further, it was the general practice to vaccinate or revaccinate contacts; some of these individuals were incubating smallpox at the time of vaccination.

Successful vaccination within 5 years of exposure provided a high level of protection against smallpox. When vaccination had been performed more than 20 years before exposure there was sometimes no residual immunity and the course of the disease was similar to that seen in unvaccinated subjects, although even then the outcome, examined statistically, was modified (Hanna, 1913).

Although its most important effect was the prevention of infection, vaccination also influenced the frequency of different clinical types of smallpox among persons who did contract the disease (see Table 1.2). Not only

was modified-type smallpox much more common among vaccinated patients (25.3% compared with 2.1% in Rao's series), but a larger proportion of ordinary-type cases was classified as discrete (83.5% compared with 47.4%) and flat-type cases were less common (1.3% compared with 6.7%). However, Rao (1972) and Guha Mazumder et al. (1975) reported that, among those who got smallpox, haemorrhagic-type smallpox was slightly more common among vaccinated than among unvaccinated subjects (see Table 1.2 and below). Not all investigators agreed with this view; for example, Sarkar et al. (1972) reported that in a series of 170 cases no cases of haemorrhagic-type smallpox occurred among vaccinated persons, but 32 cases occurred in unvaccinated subjects. Except in modified-type smallpox, which was hardly ever fatal, and haemorrhagic-type, which was almost always fatal, the case-fatality rates were lower in vaccinated than in unvaccinated patients (see Table 1.2).

Vaccination resulted in the modification of three aspects: the toxaemia (and correspondingly the case-fatality rate), the number of lesions, and the character and evolution of the rash. The waning of vaccine protection against these manifestations did not occur uniformly.

Effects of Vaccination on Toxaemia

The initial constitutional symptoms of smallpox were associated with the replication of variola virus during the incubation period, the end of which was marked by the sudden onset of fever and headache that accompanied the secondary viraemia. In some cases vaccine protection had little apparent effect on symptoms of fever and headache at the end of the incubation period, but no skin lesions developed; the patient was said to have suffered from variola sine eruptione, which was occasionally associated with pneumonitis. Sometimes the pre-eruptive stage in vaccinated subjects was accompanied by a fleeting erythematous rash that particularly affected the flexures.

The more toxic forms of smallpox, except for the haemorrhagic type, were much less common in vaccinated than in unvaccinated subjects (see Table 1.2).

Effects of Vaccination on the Number of Lesions

The skin lesions were initiated by the infection of dermal capillaries by virus released into the circulation during the secondary viraemia (see Chapter 3). Prior vaccination usually reduced the level of viraemia and thus the opportunity for skin lesions to develop; variola sine eruptione occurred mainly in vaccinated persons, and confluent lesions were much less common among vaccinated subjects. In Rao's series 16.5% of vaccinated patients who had ordinary-type smallpox were classified as confluent or semi-confluent, compared with 52.6% of unvaccinated patients.

Effects of Vaccination on the Character and Evolution of the Rash

In some cases of smallpox in vaccinated subjects the character and rate of evolution of the rash differed from the usual pattern, presumably because of the anamnestic response initiated by infection with variola virus in the vaccinated subject. The individual lesions were more superficial and hence did not have the "shotty" feel, and their edges were often irregular. Umbilication and loculation were not found in these superficial lesions, which resembled those of chickenpox. Often the modified lesions were very small, but they could vary quite considerably in size in any particular area of skin (Plate 1.19C). In fair-skinned subjects the red areola around the pustules was often more pronounced—presumably an allergic manifestation. In many vaccinated subjects the rash also evolved more rapidly so that the lesions passed through the stages of macule, vesicle and pustule in 3 or 4 days instead of 7 or 8. On the other hand, many field workers found no such differences in symptomatology, apart from a greater frequency of cases of ordinary-type smallpox with few skin lesions. Smallpox in vaccinated subjects who did contract the disease was no different in other respects from that found in unvaccinated patients. Mack et al. (1970), in cases with similar lesion density, found no differences that could be related to vaccination status in the length of the pre-eruptive stage, the rate of maturation of skin lesions, the occurrence of corneal lesions, the case-fatality rate or the prevalence of residual pockmarks.

Effects of Vaccination in Variola Minor

In Marsden's series, variola minor occurred in 1756 patients who showed evidence of having been successfully vaccinated, out of a total of 13 686 cases. In only 2 of these was there evidence of vaccination within the previous 5 years and in only 7 within the previous 10 years; the great majority had been vaccinated 20 or more years earlier. In an epidemic in the Netherlands, Jong (1956) found no cases in persons vaccinated less than 30 years before, and, in Brazil, Suzart de Carvalho Filho et al. (1970) found a vaccine-efficacy ratio of 94%, regardless of the interval since previous vaccination (see Chapter 12). Vaccination thus provided very good protection against variola minor, a conclusion which is in keeping with the experience of epidemiologists working in Ethiopia and Somalia during the global smallpox eradication programme.

LABORATORY FINDINGS

Laboratory observations on cases of smallpox will be described in Chapter 3, as part of an attempt to build up a coherent picture of the pathogenesis of the disease. However, it is useful to examine some of the results here in the context of the symptomatology of smallpox.

Virological Observations

The principal value of the laboratory, without which it would have been impossible confidently to certify global smallpox eradication, was the demonstration of the presence or absence of variola virus in vesicle fluid and crusts from suspected cases of smallpox (see below). This section reviews virological findings made on cases of smallpox which may help to explain the clinical signs and symptoms.

Viraemia

According to the model for the pathogenesis of variola developed in Chapter 3, there was an early transient viraemia soon after infection. The virus then replicated in the lymph nodes, spleen and bone marrow until just before the onset of symptoms, which was associated with secondary viraemia. All the reported observations of viraemia in smallpox relate to this "secondary" viraemia.

Precise observations were never made on the distribution of variola virions among the various components of the blood (plasma, leukocytes and erythrocytes); by analogy with other poxvirus infections viraemia would have been expected to be primarily cell-associated (see Chapter 3). However, most observations that were made on the blood of smallpox patients utilized either serum or lysed whole blood, the material being inoculated either into monkeys (Kyrle & Morawetz, 1915) or on the chorioallantoic membrane of chick embryos (Downie et al., 1950, 1953, 1969b; Mitra et al., 1966). In haemorrhagic-type smallpox both serum and lysed blood gave positive results; it is possible that viraemia might have been detected more readily in cases of ordinary-type smallpox if separated leukocytes had been examined.

However, the general pattern appears to have been consistent. Although viraemia must always have occurred, virus was only rarely recovered from the blood or serum from cases of ordinary-type smallpox. Downie et al. (1950, 1953) and Mitra et al. (1966) recorded one or two positive results out of many attempts in such cases and then only in the early days of the disease. The picture in haemorrhagic-type smallpox was quite different. Virus was readily recovered from the blood of all cases, the titres were usually high, as determined by titration on the chorioallantoic membrane of chick embryos (Downie et al., 1953, 1969b; Mitra et al., 1966; Sarkar et al., 1969), and viraemia usually persisted until the patient died. Downie et al. (1969b) noted that viraemia was consistently much higher in cases of early than of late haemorrhagic-type smallpox. Patients with haemorrhagic-type smallpox usually also had soluble antigens in their bloodstream (antigenaemia), the level of which was roughly correlated with the level of the viraemia. Although few opportunities occurred for its practical use, the demonstration of antigen in the serum provided a useful and rapid laboratory diagnostic test for haemorrhagic-type smallpox, a disease in which the differential diagnosis was extremely difficult, especially in non-endemic countries, in which it would rarely have been suspected.

Thus haemorrhagic-type smallpox appears to have been associated with overwhelming infection and the continued release of virus from infected cells into the bloodstream; in

other cases demonstrable viraemia was usually restricted to the pre-eruptive and early eruptive stages of the disease.

Skin

Variola virus could be readily demonstrated in the skin lesions of all cases of smallpox, from the earliest stages of the rash until the scabs separated. The large amount of virus in the vesicle fluid was eventually included within the scabs. However, because virus in the scabs was associated with large flakes of inspissated material it appeared to be relatively unimportant as a source of infectivity for contacts, compared with virus in the oropharyngeal secretions (see Chapter 4). In spite of the absence of vesicles or pustules, the skin of cases of haemorrhagic-type smallpox contained very large numbers of virions.

Oral and pharyngeal mucous membranes

The earliest focal lesions in smallpox occurred in the oropharynx, and instead of forming papules and vesicles, as in the skin, these lesions soon ulcerated and thus liberated large amounts of virus into the saliva. This was the major source of infectious virus as far as the transmission of smallpox was concerned (see Chapter 4).

Conjunctiva

Patients with smallpox sometimes had conjunctivitis. Virus could be readily recovered from the conjunctival swabs of patients in whom conjunctivitis developed early in the course of the disease, but usually not from convalescent patients who developed conjunctivitis (Dekking et al., 1967; Kempe et al., 1969; Sarkar et al., 1973a). The occasional appearance of variolous conjunctivitis at or before the onset of fever suggested to Kempe et al. (1969) that the conjunctiva may have been the portal of entry in these cases.

Urine

The interpretation of the results of testing urine for virus was difficult, since patients often had pustules on the skin near the urethral orifice, and catheterization, had it been possible to do this aseptically, was not ethically justifiable. However, viruria was recorded by all investigators who tested the urine from cases of variola major. Positive results were recorded by Downie et al. (1965a) in 17 out of 34 specimens, and by Sarkar et al. (1973a) in 21 out of 39. The viruria was greater in degree and more persistent in severe cases (haemorrhagic-type smallpox and those with a confluent rash) than in milder cases. No virus was detected in the urine of some cases whose severity was comparable to that of cases with viruria.

Serological Observations

The immune response in generalized orthopoxvirus infections (including smallpox) is described in Chapter 3; this section summarizes information on the correlation between various serological responses and the clinical severity of smallpox, to the extent that such information is available. Unfortunately, there is an almost complete lack of data on cell-mediated immunity in smallpox, an immune response that was probably of critical importance in the pathogenesis and immunopathology of the disease.

The most comprehensive studies on the serological responses in cases of smallpox are those reported by Downie et al. (1969a,b) on ordinary-type and haemorrhagic-type smallpox, using haemagglutination-inhibition, complement-fixation, gel-precipitation and neutralization tests. In most cases of non-fatal ordinary-type smallpox, antibody was detected by haemagglutination-inhibition and neutralization tests between the 6th and 8th days after the onset; by complement fixation and gel precipitation about 2 days later (Fig. 1.4). The antibody response was slower and

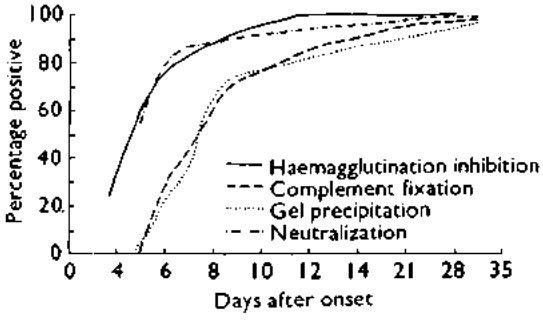


Fig. 1.4. Percentages of positive antibody titres obtained at various times after the onset of ordinary-type variola major, by 4 types of serological test, in 151 subjects of whom 127 had been vaccinated, usually many years before. (From Downie et al., 1969a.)

the titres were lower in early haemorrhagic-type smallpox than in other cases (Sarkar et al., 1967, 1969), but Downie et al. (1969b) found haemagglutinin-inhibiting antibodies in most cases of haemorrhagic-type smallpox, although both neutralizing and complement-fixing antibodies were at much lower levels or absent in such cases.

As might be expected, antibodies usually appeared earlier and reached higher levels in vaccinated than in unvaccinated patients (Downie & McCarthy, 1958).

Haematological Observations

The blood picture in smallpox varied according to the nature of the case and the stage of the disease. In most cases there was little change in the red blood cell count, but during the eruptive stage the numbers of granular leukocytes usually fell and a relative and absolute increase in the numbers of lymphocytes occurred. The granulocytopenia was often reversed during the late pustular stage, perhaps because of secondary infection of the skin lesions in some cases.

In early haemorrhagic-type smallpox there was often a striking change in the blood picture, which Ikeda (1925) considered to be of diagnostic value. Pathological forms of normoblasts with basophil stippling or polychromatophilia were common; the total leukocyte count was increased by 30–40%, with a marked augmentation in the numbers of lymphocytes and monocytes; and the presence of myelocytes and myeloblasts suggested an intense stimulation of the bone marrow. In contrast to the rise in the number of platelets found after the vesicular stage in many other cases of smallpox, Ikeda discovered that there was a marked and progressive thrombocytopenia in haemorrhagic-type smallpox, the number of circulating platelets often falling to a very low level.

Sarkar et al. (1968) compared the concentrations of various serum proteins in 28 sera from cases of smallpox of different clinical severity with those of an equal number of normal subjects. The total proteins were unchanged, but albumin was diminished and globulin increased, the increase being associated with fractions α_2 and γ. There was no correlation between the concentrations of any of these proteins and the level of haemagglutinin-inhibiting antibodies.

More detailed studies of the pathophysiology of bleeding were carried out on patients in Madras and reported by McKenzie et al. (1965) and Roberts et al. (1965). Their findings in relation to vascular integrity, platelet function and blood coagulation are summarized in Table 1.8, which illustrates the generality of impaired functions in haemorrhagic smallpox, especially evident in the early type. In contrast to Ikeda (1925), these

Table 1.8. Results of tests for platelet function, vascular integrity and blood coagulation in smallpox[a]

Test	Ordinary-type smallpox (8 patients)	Haemorrhagic-type smallpox (35 patients)	
		Early	Late
Bleeding time (Ivy):			
0–9 minutes (normal)	7	0	0
10–19 minutes	0	0	2
⩾20 minutes	1	12	21
Tourniquet test:			
Negative	8	0	7
Positive	0	13	17
Clot retraction:			
Good	7	0	0
Poor	2	6	7
Nil	0	5	18
Venous clotting time:			
0–9 minutes (normal)	8	3	7
10–14 minutes	0	6	13
⩾20 minutes	0	3	5
Euglobulin fibrinolysin test:			
1.5–3 hours (normal)	2	2	3
4 hours	6	1	6
⩾5 hours	1	8	9
Platelet count per mm^3 (range) (normal: 275 000 ± 100 000)	<20 000 to 303 000	<20 000 to 128 000	<20 000 to 138 000

[a] Based on McKenzie et al. (1965).

investigators found that many patients with smallpox but with no clinical evidence of haemorrhage had moderate to severe thrombocytopenia but usually no other coagulation defect. Patients with late haemorrhagic-type smallpox had severe thrombocytopenia and some had a mild to moderate decrease in prothrombin and a moderate decrease in accelerator globulin. As expected, the cases of early haemorrhagic-type smallpox were characterized by multiple defects, with significant and specific coagulation defects in addition to severe thrombocytopenia. All had an elevated thrombin time and a total absence of accelerator globulin, which the authors ascribed to disseminated intravascular coagulation. At autopsy such cases showed disseminated intravascular thrombosis involving small vessels in many organs.

COMPLICATIONS

Complications of two kinds occurred in smallpox. One group was due either directly or indirectly to viral activity in an unusual site, the other to secondary bacterial infection.

The Skin

As noted earlier, pustulation was part of the natural sequence of development of the skin lesions in smallpox. However, in most countries in the days before antibiotics were available and, even recently, in those in which hygiene was poor and such treatment not obtainable, secondary bacterial infection of the skin lesions often occurred, sometimes to an extent that Ricketts (1908) described as "thousands of boils". In pre-antibiotic days septic complications also occurred in variola minor; Marsden (1936) recorded the presence of boils in 3.65% and of septic dermatitis in 2.3% of his series of cases. Even higher percentages of these complications were seen in the Ogaden desert during the late stages of the eradication programme in Somalia (Ježek et al., 1981).

Ocular System

Mild conjunctivitis, occurring early in the course of the disease, or at the time of the eruption if there were lesions on the eyelids, was essentially part of the acute disease and not a complication. Sometimes it was the only symptom (Dekking et al., 1967). Pocks often occurred on the margins of the eyelids but not on the avascular cornea. Often there was much swelling of the eyelids (see Plate 1.13), which made it difficult to open the eyes. Dixon (1962) suggests that it was this swelling, rather than keratitis or corneal ulceration, that accounted for the frequent references in the old non-technical literature that a person was "blind with smallpox". Corneal ulceration and sometimes keratitis did occur in smallpox. These complications were common in haemorrhagic-type smallpox, but were of relatively minor importance because such patients soon died. In ordinary-type smallpox corneal ulceration occurred at about the end of the 2nd week of illness, beginning at the corneal margin. Sometimes the ulcers healed rapidly and there was only a trivial opacity; on other occasions there was severe corneal scarring. Both Dixon (1962) and Rao (1972) note that keratitis and corneal ulceration were far more common in malnourished children than in the well nourished; for this reason these conditions continued to be more important complications in developing countries than in the more prosperous industrialized countries. Mack et al. (1970) reported that 28 out of 405 patients examined within 6 weeks of onset in a rural setting in Pakistani Punjab had corneal lesions, which occurred mostly in patients with confluent or semiconfluent rashes. Three out of 11 patients seen a year later had permanent ocular lesions, and 4 other instances of permanent lesions were observed in 148 cases in whom lesions had not originally been seen. The overall rate of residual corneal opacity in those surviving smallpox was 4.4%. Corneal ulcers occurred in 1% of cases in Rao's series (excluding haemorrhagic-type smallpox) and keratitis in about 0.25%.

Joints and Bones

Arthritis, associated with involvement of the bones of the joints, was a relatively common complication of smallpox, occurring in 1.7% of cases in Rao's series, usually in children. Cockshott & MacGregor (1958) and Cockshott (1965) reviewed the condition, which they called "osteomyelitis variolosa", and described a series of cases observed in Nigeria. More recently, Gupta & Srivasta (1973) reviewed the X-ray features of 20 cases observed in India. The elbow was the most commonly affected joint and symmetrical

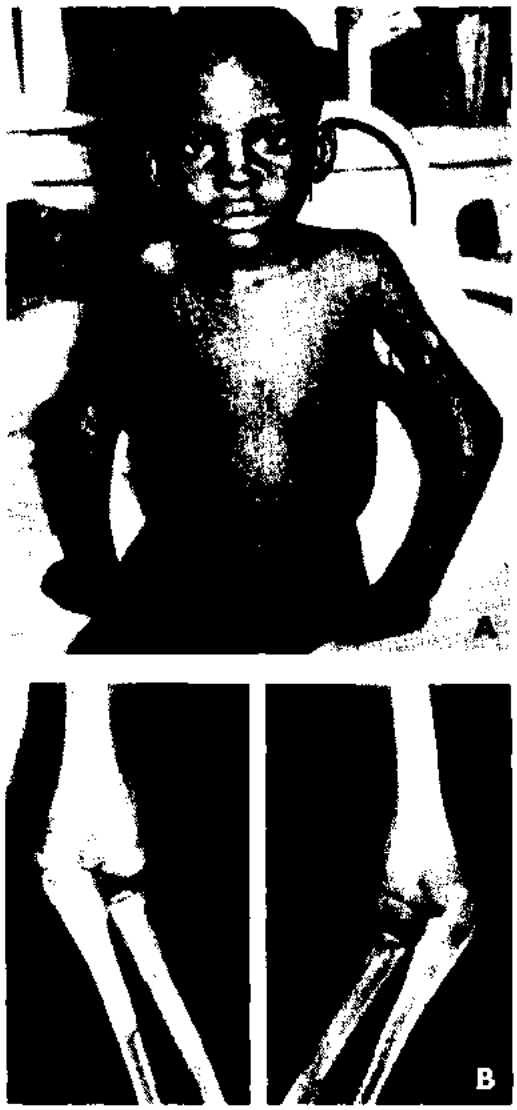


Plate 1.26. Osteomyelitis variolosa in an unvaccinated Nigerian child. Joint symptoms appeared 1 week after the onset of rash and affected both elbows. **A**: External appearance, showing hypopigmented spots of healed exanthem and swollen elbows. **B**. X-ray appearances (From Cockshott & MacGregor, 1958.)

bilateral joint involvement was frequent (Plate 1.26). Although secondary bacterial infection sometimes occurred, the disease was primarily due to viral infection of the metaphyses of growing bones. The primary bone lesion was probably a proliferating arteritis, which led to fibrosis, necrosis and bone resorption (Eeckels et al., 1964).

This complication usually occurred late in the course of the disease, after the 15th day, and was accompanied by a brief recurrence of fever during the scabbing stage. Because of the severity of smallpox itself, and the insidious nature of the bone and joint involvement, cases were often missed during the attack, and only recognized as probably having been due to smallpox years afterwards because of a variety of bone defects for which there were no other explanations (Gupta & Srivasta, 1973).

Respiratory System

Rao (1972) regarded respiratory complications as common in severe smallpox, especially in the unvaccinated. However, the symptoms he describes, bronchitis and pneumonitis, are better regarded as part of the normal disease syndrome than as complications. Pulmonary oedema was fairly common in haemorrhagic- and flat-type smallpox. Bronchopneumonia due to secondary bacterial infection sometimes occurred and could be serious in debilitated patients. In his long series of cases of variola minor, Marsden (1936) recorded only 7 cases of bronchopneumonia.

Although sometimes responsible for death, pulmonary complications were usually followed by complete recovery. However, coughing could have serious epidemiological consequences, if it occurred during the 1st week of disease, when the oral secretions were most highly infectious (see Chapter 4). A.R. Rao (personal communication, 1981) regarded cough associated with the sticky mucus of bronchitis as a relatively common symptom, especially in unvaccinated individuals. However, its epidemiological consequences were reduced if, as in the majority of cases, it did not become evident before about the 10th day of disease. Epidemiologists engaged in the global smallpox eradication programme regarded cough as a rare symptom in smallpox.

Gastrointestinal System

Apart from vomiting and, less commonly, diarrhoea during the pre-eruptive stage, gastrointestinal symptoms were rare. Diarrhoea sometimes occurred in the 2nd week and acute dilatation of the stomach was observed, especially in infants, though only rarely (Rao, 1972). Extensive viral infection of the intestinal mucous membrane occurred in some severe cases, especially in flat-type smallpox.

In such cases, which were usually fatal, portions of the mucous membrane were passed as a tubular cast.

Genitourinary System

Orchitis was uncommon (0.1% in Rao's series) and usually unilateral. This observation casts doubt on the suggestion of Phadke et al. (1973) that smallpox was the single most important etiological factor in obstructive azoospermia in India.

In haemorrhagic-type smallpox, bleeding into the pelvis of the kidney sometimes produced haematuria (see Table 1.6).

Central Nervous System

Encephalitis was a relatively common complication of smallpox (about 1 in 500 cases in variola major (Rao, 1972) and 1 in 2000 cases in variola minor (Marsden, 1936)). It usually appeared between the 6th and the 10th day, when the rash was in the papular or vesicular stage. Encephalitis contributed little to the case-fatality rate of variola major but was an important factor in the few deaths which occurred in variola minor. Recovery, although sometimes slow, was usually complete.

According to a detailed review by Marsden & Hurst (1932), the symptomatology and the pathological findings in fatal cases of encephalitis associated with variola minor were indistinguishable from those of the encephalomyelitis which occasionally occurs after vaccination or in the late stages of measles. Clinical details are described in Chapter 7, for although it was a much rarer complication (in Madras, for example, 1 in 500 cases of smallpox and 1 in 100 000 cases of primary vaccination (Rao, 1972)), postinfection encephalitis was a much more significant feature of vaccination than of smallpox, since it was then the result of medical intervention in an otherwise healthy subject rather than a rare complication of a severe disease.

SEQUELAE

In order of their frequency the sequelae seen in persons who recovered from smallpox were facial pockmarks, blindness, and limb deformities.

Pockmarks

During the first few months after recovery from smallpox the sites of the scabs were abnormally pigmented, hypopigmented in dark-skinned persons and red or hyperpigmented in fair-skinned subjects (Plate 1.27A and B). As the skin regained its normal pigmentation, most cases of variola major, but few of variola minor, were seen to have pitted scars, called pockmarks, in the sites of some of the pustular skin lesions. These were depressed scars 2 mm or more in diameter, usually circular and varying in number from one (which would be difficult to ascribe to smallpox) to several hundreds (Plate 1.27C and D). They resulted from fibrosis in the dermis, and were much more common on the face because of the greater frequency of large sebaceous glands in the skin of the face (Bras, 1952b). Although the rash occurred on the scalp as well, relatively few pockmarks were seen there. In ordinary-type variola major the rash affected the sebaceous glands severely (Bras, 1952b) and permanent facial pockmarks occurred in 65–80% of survivors (Mack et al., 1970; Ježek et al., 1978d). The sebaceous glands were not affected in flat-type smallpox and the few patients who survived this type of infection were rarely severely pockmarked.

When secondary bacterial infection of the pustules occurred the resulting scarring was often more severe and the scars more irregular in shape than after an uncomplicated rash.

In variola minor the rash, though sometimes profuse, comprised shallow lesions that were usually restricted to the epidermis and only rarely involved the sebaceous glands—hence pockmarks were much less common in such cases. For example, Marsden (1936) recorded depressed scars in only 0.7% of his series of cases, although hyperpigmentation was present in about 11% of these fair-skinned subjects at the time of their discharge from hospital. Among persons with more deeply pigmented skins, hypopigmented spots sometimes occurred on the face or elsewhere for several months after recovery (Ježek & Hardjotanojo, 1980) but eventually disappeared.

The observation of facial pockmarks was an important epidemiological tool in smallpox eradication programmes in countries in which the disease was due to variola major, but in those in which variola minor prevailed pockmarking was too infrequent for such

surveys to be of epidemiological value (see Chapters 4 and 24).

Blindness

Corneal scarring with consequent blindness sometimes followed the keratitis or corneal ulceration which was a rare complication of smallpox (though less uncommon in malnourished individuals). As Dixon (1962) commented, "Every writer on smallpox over the last 150 years has pointed out that in his experience the amount of blindness due to smallpox was much less than that quoted by previous authors". The explanation is probably that the authors quoted were almost always writing of conditions in Europe. During the last 150 years the level of nourishment and hygiene rose steadily among those who formed the subject of these publications, and, as remarked earlier, keratitis, corneal ulceration and corneal scarring rarely occurred in well-nourished patients. Blindness following smallpox remained a serious although uncommon complication in poorer countries (Plate 1.27C and D). Rao (1972) noted 60 patients with keratitis and/or corneal ulcer, of whom 24 had loss of vision in one eye and 1 in both eyes—an incidence of blindness of 0.45% among 5459 survivors. In Bangladesh, Hughes (WHO/SE/78.101) found blindness in 0.9% and corneal opacities in an additional 2.1% of patients examined 1–2 years after recovery from smallpox. All 4 cases of blindness and 7 of the 9 cases of corneal scarring occurred in unvaccinated subjects.

Limb Deformities

As has been described earlier, osteomyelitis and arthritis were not uncommon complications of smallpox. Many cases resolved without permanent deformity. Because of the severity of the disease itself and the mild symptoms of joint involvement, skeletal manifestations were often missed during the acute infection and recognized years later in the form of bone shortening, flail joints, subluxations and gross bone deformities (Gupta & Srivasta, 1973).

PROGNOSIS OF VARIOLA MAJOR

The prognosis of a case of smallpox had to be evaluated in terms of the likelihood of death and the possibilities of serious sequelae. In both respects, the prognosis of variola minor was almost invariably good; the vast majority of patients recovered and even facial pockmarks were an uncommon sequel. It is therefore necessary to consider the prognosis only in terms of variola major. As will be further elaborated in Chapter 2, there were geographical variations in the virulence of variola major virus, in terms of the usual case-fatality rates in different parts of the world, which during the period of the Intensified Smallpox Eradication Programme (see Chapter 10) seemed to be uniformly high in the Indian subcontinent and adjacent parts of western Asia and rather lower in Indonesia and western, central and eastern Africa.

Calculation of Case-Fatality Rates

How representative were hospital-based data?

The calculation of the case-fatality rate in smallpox was not a straightforward matter. Most data (e.g., Rao, 1972; Guha Mazumder et al., 1975) were based on series of cases treated in hospitals; the question arises of how representative of the total spectrum of cases were those admitted to hospital. Rao's (1972) series was probably representative of cases in Madras; in a personal communication (1981) this author states that between 1961 and 1969, 80–90% of all cases in Madras were admitted to the city's Infectious Diseases Hospital, the proportion between 1965 and 1969 being almost 100%.

This was not true of other areas, especially where rural populations were involved. Koplan et al. (1978) investigated this problem in Bangladesh, from which smallpox had been eliminated in 1970 only to be reintroduced by refugees returning from India in 1972. Table 1.9 compares the age- and sex-specific case-fatality rates pertaining to 346 cases admitted to the Dhaka Infectious Diseases Hospital during the period March 1972 to April 1973 with those of 502 non-hospitalized cases diagnosed by specially trained surveillance teams in a rural area in the Noakhali District in south central Bangladesh during the period July 1972 to February 1973. The age and sex distributions of the two sets of data are very

Table 1.9. Age- and sex-specific case-fatality rates of 346 hospitalized smallpox patients and 502 non-hospitalized rural smallpox cases in Bangladesh[a]

Age group (years)	Male		Female		Total	
	Number	Case-fatality rate (%)	Number	Case-fatality rate (%)	Number	Case-fatality rate (%)
Dhaka Infectious Diseases Hospital:						
0–4	49	59	39	67	88	63
5–14	41	39	41	34	82	37
15–34	90	54	43	47	133	52
35–54	28	50	11	55	39	51
⩾55	3	67	1	100	4	75
Total	211	52	135	50	346	51
Noakhali District:						
0–4	47	34	45	33	92	34
5–14	68	18	82	13	150	15
15–34	98	18	45	18	143	18
35–54	41	24	42	21	83	23
⩾55	14	29	20	15	34	21
Total	268	22	234	20	502	21

[a] Based on Koplan et al. (1978).

similar; when the rates were applied to a standard Bengali population the overall case-fatality rates were only changed from 51% to 52% for the hospitalized patients and from 21% to 23% for the village patients, a highly significant difference between the two sets of data.

The explanation is complex and lies in a number of factors which would probably differ in importance in different places, but which must always be borne in mind when considering case-fatality rates based on hospitalized series of cases in countries in which smallpox was endemic. In Bangladesh, hospital admission reflected a high proportion of patients who were too ill to travel back to their villages or too sick to hide their illness within the community, whereas the village data essentially referred to every case in the community.

Effects of Immunity

Immunity after an attack of smallpox

A person who had recovered from smallpox had a high degree of immunity to reinfection, which usually lasted throughout life, but

Table 1.10. Protection against challenge vaccination with vaccinia virus among persons who had recovered from smallpox[a]

Time since attack of smallpox	Number test vaccinated		Major reaction (%)[b]
	Vaccination scar[c]	Number	
< 6 months	..	21[d]	0
6–12 months	+	60[d]	6
	−	62[d]	19
12 months (variola minor)	−	65[e]	63
⩽5 years	..	64[f]	8
6–11 years	..	156[f]	50
12–17 years	..	86[f]	50
⩾18 years	..	119[f]	78

[a] Variola major unless otherwise indicated.
[b] Major reaction = primary type of reaction with vesicle 1 week after vaccination; or, more commonly, revaccination type, with vesicular or pustular lesion or area of induration surrounding a central scab or ulcer, after 6–8 days.
[c] .. = data not recorded.
[d] Data from Zikmund et al. (1978).
[e] Data from Ježek et al. (1981).
[f] Data from Vichniakov (1968).

second attacks did occasionally occur. Rao (1972) noted about 1 repeat attack per 1000 cases, the average interval between the attacks being 15–20 years. This refers to clinical disease, confirmed by laboratory investigation, in pockmarked persons. Serological examination of exposed contacts would probably have revealed that second subclinical infections were much more common; subclinical infection was not uncommon in vaccinated contacts (Heiner et al., 1971a). However, subclinical infections were of little epidemiological importance, except as boosters of immunity, since subjects with such infections did not transmit them.

Another measure of the persistence of resistance following smallpox was provided by determining the response of persons known to have had smallpox to challenge vaccination with vaccinia virus. Interpretation of the results (Table 1.10) is complicated by the fact that many of those who had had variola major had also been vaccinated, a procedure which enhanced immunity to challenge vaccination (Zikmund et al., 1978). A substantial proportion of persons exhibited a major response to vaccination as early as 1 year after recovery from variola minor, and even after variola major resistance to challenge vaccination was low in half the subjects tested 6–11 years after recovery from the disease. In variola major immunity to challenge vaccination persisted for much longer in those who had had a severe attack of smallpox than in those who had suffered only a mild attack (Vichniakov, 1968). As far as heterologous immunity is concerned, it appears that vaccination protected against naturally transmitted smallpox (see below and Chapter 7) rather more effectively than smallpox modified the response to vaccination. This may have been mainly due to the dose of virus and the manner of its implantation: a large dose introduced into the skin in vaccination and a small dose implanted on the respiratory mucosa in smallpox.

Immunity after vaccination

The effects of vaccination on preventing infection will be discussed in Chapters 7 and 11; here we are concerned with the effects of vaccination and/or revaccination on the severity of smallpox in vaccinated persons who did contract the disease. There are several difficulties in evaluating these effects. There were some patients who said that they had been vaccinated (or revaccinated) but had no scar; Rao (1972) classed these as "unsuccessfully vaccinated". However, even in Madras some of these persons may have been successfully vaccinated, with vaccine of low potency applied over a small area of skin, leaving no scar; such misdiagnoses of vaccination status may account for the difference in prognosis between the "unvaccinated" and the "unsuccessfully vaccinated" in Rao's data (case-fatality rates in ordinary-type smallpox of 36.9% and 27.2% respectively). Among those with a vaccination scar there were other problems. First, did the scar really result from the replication of vaccinia virus in the skin? Secondary infection without viral replication could cause scars, especially when the rotary lancet was used with an unsatisfactory liquid vaccine. Secondly, how long ago did the last successful vaccination (or revaccination) occur? These questions could not always be accurately answered, but it is important to bear them in mind when considering the effects of vaccination on the prognosis of smallpox. Finally, the studies of Heiner et al. (1971a) showed that in endemic areas subclinical infection with variola virus occurred rather frequently among vaccinated persons, thus boosting their immunity.

Data published by Hanna (1913) from an outbreak of variola major in Liverpool, England, in 1902–1903, illustrate clearly the ameliorating effect of childhood vaccination on the severity of smallpox (Table 1.11). There was a striking difference between vaccinated and unvaccinated patients in all age groups, both in the spectrum of severity and in case-fatality rates. Protection waned with age—i.e., with increasing intervals since vaccination—but was substantial even in those aged more than 50 years.

Rao's data (see Table 1.2) confirm the extent of the protection against death provided by vaccination; the overall case-fatality rates in vaccinated and unvaccinated (including "unsuccessfully vaccinated") persons in his series were 6.3% and 35.5% respectively.

Hanna's conclusions on the duration of protection against death provided by vaccination, in those who got smallpox, is confirmed by data collected by Mack (1972), who analysed 680 cases of variola major occurring after importations of the disease into Europe and Canada during the period 1950–1971 (Table 1.12). The case-fatality rate was 52% in unvaccinated persons, 1.4% in those vaccinated 0–10 years before exposure, and only

Table 1.11. Effect of vaccination in infancy on the severity and case-fatality rates in variola major, according to age groups[a]

Age group (years)	Vaccination in infancy	Severity			Number of deaths	Total	
		Mild	Moderate	Severe		Number of cases	Case-fatality rate (%)
0–4	+	7	0	0	0	7	0
	–	6	24	25	25	55	45.0
5–14	+	85	11	0	0	96	0
	–	15	34	8	6	57	10.5
15–29	+	338	91	7	3	436	0.7
	–	12	41	19	10	72	13.9
30–49	+	226	101	22	13	349	3.7
	–	1	8	15	13	24	54.2
⩾50	+	30	21	4	3	55	5.5
	–	3	3	6	6	12	50.0
All ages	+	686	224	33	28	943	3.0
	–	37	110	73	60	220	27.2
Total		723	334	106	88	1 163	7.6

[a] Data from an outbreak in Liverpool, England, in 1902–1903, analysed by Hanna (1913).

Table 1.12. Age and vaccination status of cases of variola major occurring after importations into western countries during the period 1950–1971[a]

Successfully vaccinated	Number of cases (deaths) by age group (years)				Total	
	0–9	10–49	⩾50	Unknown	Number of cases (deaths)	Case-fatality rate (%)
Never	30 (12)	37 (18)	11 (10)	1 (1)	79 (41)	52
Only after exposure	20 (4)	41 (13)	9 (3)	0	70 (20)	29
0–10 years before exposure	18 (0)	48 (1)	5 (0)	1 (0)	72 (1)	1.4
11–20 years before exposure	0	40 (3)	3 (0)	0	43 (3)	7
>20 years before exposure	0	187 (8)	96 (25)	14 (0)	297 (33)	11
Unknown	24 (2)	50 (5)	24 (5)	21 (0)	119 (11)	9
Total	92 (18)	403 (47)	148 (43)	37 (1)	680 (109)	16

[a] Based on Mack (1972).

11% in those vaccinated over 20 years before exposure. The contrast is even more striking if only the age group 10–49 years is considered: a case-fatality rate of 49% in the unvaccinated and one of 4.3% in those vaccinated over 20 years earlier.

Before 1967 it was a common practice in India, as it had earlier been in Great Britain and elsewhere, to make several insertions of vaccinia virus at adjacent sites. Early in the Intensified Smallpox Eradication Programme it was decided that vaccination should routinely be carried out on one site only (see Chapter 11), but some older data suggested that there was a correlation between protection and scar area (allowing for changes in the area with growth) and/or the number of insertions. For example, Hanna (1913) reported that the mildest attacks of smallpox occurred in those with the largest scar areas, while at all ages the average scar areas of vaccinated contacts who did not get smallpox was substantially larger than in those who did. Likewise, Rao (1972) reported a case-fatality rate of 16.4% among 79 cases of ordinary-type smallpox in persons aged 0–9 years with only 1 scar, compared with no deaths among 70 cases in comparable individuals with 2, 3 or 4 scars.

Passive immunity

Apart from reports of the deliberate use of anti-orthopoxvirus serum for serotherapy, some information has been gathered on the effects of passive immunity resulting from the

Table 1.13. Age-specific case-fatality rates of smallpox in unvaccinated persons in India

Age groups (years)	India, 1974–1975[a,b]		Madras, 1961–1969[b,c]	
	Number of cases	Case-fatality rate (%)	Number of cases	Case-fatality rate (%)
0–4	725	45.7	2 091	41.7
5–9	605	15.5	708	22.2
10–14	292	5.8	154	11.7
15–19	72	15.3	143	22.4
20–29	115	22.6	260	39.2
30–39	78	23.1	91	44.0
40–44	..	..	32	37.0
40–49	39	30.8	..	..
⩾45	..	..	55	61.5
50–59	26	26.9	..	..
⩾60	19	31.6	..	..
Total	1 971	26.5	3 544	35.5

[a] Data collected from 4 endemic and 2 low incidence states (Basu et al., 1979).
[b] .. = data not recorded.
[c] Hospitalized patients in Madras (Rao, 1972).

vaccination of pregnant women during the incubation period of smallpox on the resistance of the fetus and the newborn child. Pregnant women were particularly susceptible to the effects of smallpox (see below), and abortion often occurred. Nevertheless, it was found that some women who had been vaccinated during the incubation period of their attack went to term and bore live babies who were usually resistant to smallpox, presumably because of passive immunization.

Effects of Age

Smallpox affected persons of all ages; the age incidence of the disease in endemic countries reflected the particular epidemiological characteristics of the population at the time (see Chapter 4). Some relevant data on the relation of age to prognosis in cases of variola major occurring in unvaccinated subjects are provided in Tables 1.9 and 1.11; additional statistics from India are shown in Table 1.13 and data for Pakistan are given by Mack et al. (1970). All these figures accord with the general impressions of most epidemiologists with extensive experience of smallpox and are consistent with the usual pattern of age-related susceptibility to death from acute infectious diseases (Burnet, 1952). Mortality was very high (usually over 40%) in infants, fell to its lowest level in children, and then rose with increasing age. The low case-fatality rate in unvaccinated children is significant in that the famous variolators in Great Britain during the 18th century, such as the Suttons, selected healthy children for this procedure (Razzell, 1977b), which may partly account for the low mortality it caused.

Such deaths as did occur in variola minor were predominantly in very young children. Suzart de Carvalho Filho et al. (1970) recorded an overall case-fatality rate of 0.8% in Brazil in 1968–1969, but the rate was 16.7% among patients aged less than 3 months and 2% in the age group 3–12 months (see Chapter 12, Table 12.16).

Effects of Pregnancy

It is universally agreed that smallpox was more severe in pregnant women than in non-pregnant women or in men, irrespective of vaccination status. Table 1.14 sets forth the distribution of clinical types of smallpox in Rao's series, in pregnant and non-pregnant women and in men in the age group 15–44 years, according to vaccination status. Although pregnant women constituted only 11.6% of the series, 50% of the cases of haemorrhagic-type smallpox occurred among them, mostly in women who had been vaccinated in infancy; indeed, almost one-quarter of all cases of smallpox in pregnant women were of the haemorrhagic type. Flat-type smallpox was over twice as common among pregnant women (3.4% compared with 1.5%) whereas modified-type smallpox was less than half as frequent (9.4% compared with 21.2%).

The effects of smallpox on the fetus or the newborn infant were also severe (Table 1.15) but congenital smallpox was not often diag-

Table 1.14. Distribution of principal clinical types of smallpox in pregnant and non-pregnant women and in men in the age-group 15–44 years, as related to vaccination status[a]

Vaccination status	Pregnancy status	Number of cases[b]	Clinical type (number of cases)			
			Ordinary	Flat	Haemorrhagic	Modified
Unvaccinated	Pregnant women	10	5	0	5	0
	Men and non-pregnant women	38	36	1	1	0
Unsuccessfully vaccinated	Pregnant women	60	39	3	18	0
	Men and non-pregnant women	416	365	18	28	5
With primary vaccination scars	Pregnant women	299	198	10	58	33
	Men and non-pregnant women	2 364	1 712	24	54	574
With primary and revaccination scars	Pregnant women	13	7	0	3	3
	Men and non-pregnant women	100	59	0	2	39
Total	Pregnant women	382 (11.6%)	249 (65.2%)	13 (3.4%)	84 (22.0%)	36 (9.4%)
	Men and non-pregnant women	2 918 (88.4%)	2 172 (74.4%)	43 (1.5%)	85 (2.9%)	618 (21.2%)

[a] Based on Rao (1972).
[b] Excludes 29 persons given primary vaccination after exposure; 2 pregnant women among these had ordinary-type smallpox.

Table 1.15. The effect of smallpox on the outcome of pregnancy[a]

	Clinical type			
	Ordinary	Flat	Haemorrhagic	Modified
Number of cases[b]	251 (14%)	13 (85%)	84 (94%)	36 (0%)
Died before termination of pregnancy	4	3	29	0
Pregnancies ended during the course of the disease:[c]	125 (51%)	9 (90%)	54 (98%)	9 (25%)
Abortions	33	0	19	0
Stillbirths (premature)	12	1	9	1
Stillbirths (full term)	4	0	5	0
Live births (premature)	26	2	6	1
Live births (full term)	50	6	15	7

[a] Based on Rao (1972).
[b] Figures in brackets indicate case-fatality rates.
[c] Figures in brackets indicate percentages of cases.

nosed among those born alive. Ten cases were recognized among the live births in Rao's series, but because their mothers had died many infants also died within a few days of birth and it was not determined whether they had smallpox or not. Smallpox caused premature termination of the pregnancy in 75% of women who got the disease during the early weeks of pregnancy and in 60% of those who contracted it after the fetus had become viable but before it had reached full term.

Clinical Type of Disease

Whether flat- or haemorrhagic-type smallpox developed in particular persons depended to some extent on the physiological factors just discussed, but clinical type provided much the best basis for the prognosis of individual cases. Haemorrhagic- and flat-type smallpox were almost always fatal and among cases of ordinary-type smallpox the extent of the rash (confluent, semiconfluent or discrete) was of prognostic value. Modified-type smallpox was very rarely fatal.

DIFFERENTIAL DIAGNOSIS

The problems involved in the diagnosis of smallpox during an epidemic or in a situation in which the disease was endemic were of a

different nature from those in suspected importations into non-endemic countries or regions. There were three elements in the diagnosis: clinical, epidemiological, and laboratory. No one diagnostic approach was always sufficient in itself. The clinical diagnosis of ordinary-type smallpox after the rash had developed was not difficult, and most cases were of this kind. But there were often patients in whom an accurate diagnosis could not be made on clinical grounds alone, at any rate at the first examination, early in the course of the disease. In such cases the epidemiological circumstances of the suspected case often provided a valuable lead. Nor was it wise to trust implicitly a positive report from the laboratory, if it ran counter to clinical and epidemiological evidence. Like everyone else, laboratory workers sometimes made mistakes, and clerical errors were always a possibility.

The clinical diagnosis of the great majority of cases of smallpox rested on the characteristic features of the pre-eruptive fever, the order of appearance of the rash (first on the face, then on the forearms, trunk and lower limbs), the evolution of the individual lesions, from macule to vesicle and pustule, and the appearance and feel of the vesicle and pustule. Furthermore, the lesions on any particular part of the body were all at more or less the same stage of development. The distribution of the skin lesions was also of great diagnostic value, with relatively few lesions on the trunk but many on the face and arms (more on the extensor than the flexor surfaces) and on the lower limbs, and on the palms of the hands and the soles of the feet. The major difficulties in differential diagnosis of ordinary-type smallpox arose in cases modified by vaccination, in which the lesions were often sparse and abnormal in appearance and underwent an accelerated course of evolution.

The diagnosis of flat-type smallpox was also relatively straightforward, but haemorrhagic-type smallpox, especially the early subtype and both forms in the early stages, was usually impossible to diagnose without laboratory assistance, and the diagnosis was often missed in non-endemic situations in which smallpox was not thought of by the attendant physician.

Diagnosis of smallpox in the pre-eruptive stage was impossible on clinical grounds alone, although it would have been suspected if epidemiological considerations (exposure to a known case, lack of vaccination) had been suggestive. The differential diagnosis of smallpox at this stage of the disease will therefore not be discussed here.

Ordinary- and Flat-Type Smallpox

The diseases involved in the differential diagnosis of ordinary- and flat-type smallpox were essentially those causing fever with rash.

Human monkeypox

Although a rare disease, human monkeypox ranks first among the diseases that might be confused with smallpox, because differential diagnosis was impossible on clinical grounds alone, although gross lymphadenopathy was found in most cases of monkeypox and not in smallpox (see Chapter 29). In the field, diagnosis depended on the occurrence of a disease indistinguishable from ordinary-type smallpox in the appropriate epidemiological situation: a particular geographical area (western and central Africa), no endemic smallpox, and the appropriate environmental surroundings (a small village in a tropical rain forest). Laboratory confirmation was essential, either by recovery of the virus from lesion material or retrospectively by appropriate serological tests.

Chickenpox

This disease of world-wide occurrence was the single most important infection to be considered in the differential diagnosis and was particularly important in three circumstances: in countries in which variola minor was endemic, in vaccinated individuals, and in situations in which chickenpox occurred rather frequently in adults, often as a severe disease, as in several parts of India. For example, in post-eradication searches in India in 1976, 63% of the "suspected smallpox" cases were in fact cases of chickenpox (Jeżek et al., 1978e).

In the usual case of chickenpox the nature, distribution and evolution of the rash are quite distinctive (Plate 1.28). The skin lesions in chickenpox are much more superficial than they were in smallpox. They appear in "crops" so that at any time lesions of various ages may be found on the same part of the body and their distribution is "centripetal" (denser on the trunk than the face and extremities) rather than "centrifugal", as in smallpox.

Plate 1.27. Sequelae of smallpox. Shortly after recovery the sites of pustules are usually depigmented in dark-skinned subjects (**A**) or red in fair-skinned subjects (**B**). Most cases of variola major leave facial pock marks, which may be deeply pigmented (**C**); blindness is a rare complication (**C** and **D**). (**B** from Herrlich et al., 1967.)

Plate 1.28. Chickenpox. On the 3rd day of rash (**A**, **B** and **C**) pocks are at different stages of development: papules, vesicles, pustules and scabs. On the 7th day of rash (**D**) all pocks are scabbed. There are many lesions on the trunk (**B**) and few on the limbs.

Plate 1.29. A: Measles. There is a blotchy generalized rash, as well as a runny nose and sore eyes. **B:** Secondary syphilis. The rash had a different distribution from that of smallpox, did not feel "shotty" and did not progress to pustules and scabs as in smallpox. (From Lambert & Farrar, 1982). **C:** Erythema multiforme.

T. H. REA

Plate 1.30. **A** and **B:** Drug eruptions, which sometimes occurred in patients with smallpox. **C** and **D**: Meningococcal septicaemia, which could be difficult to differentiate from early haemorrhagic-type smallpox. (**B, C, D** from Lambert & Farrar, 1982.)

Difficulties arose with severe chickenpox in adults (White, 1978), a disease found especially in some parts of India (Kerala, Tamil Nadu (formerly Madras State), and West Bengal). Indeed, some severe cases of chickenpox in adults were associated with such an extensive rash, including lesions on the palms and soles, that it was impossible to be certain at any stage of the disease as to whether it was chickenpox or smallpox. During the eradication programme, all such cases were regarded as smallpox and appropriate control measures were undertaken. Sometimes the lesions in this type of chickenpox were haemorrhagic, and it was in these cases that the rate of development of the rash and its distribution were important diagnostic features.

Such severe cases of chickenpox have always been rare. Diagnostic problems occurred more frequently between attacks of chickenpox of ordinary severity and mild, particularly vaccine-modified, attacks of smallpox. In vaccine-modified smallpox the lesions were often superficial, not "shotty"; they dried up quickly with a small scab and left scars very little different from those of chickenpox. Differential diagnosis was often impossible on clinical grounds alone; laboratory confirmation was essential.

Since they had the same seasonal incidence, smallpox and chickenpox might sometimes have been expected to occur concurrently in the same patient. Sarkar et al. (1976) report 3 such cases from a refugee camp near Calcutta in 1972, in males aged 15, 30 and 60 years respectively, all with vaccination scars. All the patients survived, the clinical course of each disease being unaffected by the other. The diagnosis of smallpox was confirmed in every case by the examination of material from variola-like lesions, and varicella virus was detected by electron microscopy in vesicle fluid from a chickenpox-like lesion in the one case that was examined by this technique.

Tanapox

This poxvirus disease occurs as a zoonosis in parts of Kenya and Zaire, and probably elsewhere in Africa (see Chapter 29). The lesions are usually single, and few in number if they are multiple. They are nodular rather than pustular and evolve much more slowly than the lesions of smallpox. However, when first seen, such lesions could be confused with those of mild smallpox in a vaccinated subject. The slow course and absence of pustulation would subsequently clarify the diagnosis. Electron microscopic examination of lesion material reveals virions similar to those of variola virus. However, tanapox cannot be cultivated on the chorioallantoic membrane.

Measles

In the first 2 days of the rash, before vesicles developed, the most likely cause of confusion was measles (Plate 1.29A), and this difficulty could persist for several more days in flat-type smallpox, although the severity of this disease was much greater than that of measles. The presence of Koplik's spots was, of course, diagnostic of measles, and in any case the difficulty disappeared as the rash evolved. Historically, measles did not present a problem in countries with endemic smallpox, but in non-endemic countries an early case of smallpox was sometimes diagnosed as measles, with possibly serious consequences in terms of secondary cases. On the other hand, in countries in which smallpox was endemic, physicians were often prone to diagnose all outbreaks of rash associated with deaths as smallpox and to report them as such to the health authorities. Some of these outbreaks later proved to be due to measles.

Syphilis

Earlier writers, e.g., Councilman (1907) and Ricketts (1908), paid considerable attention to syphilitic rashes as presenting a problem in differential diagnosis. With the advent of penicillin and the consequent reduction in the incidence of syphilis—especially of secondary syphilis—in the developed countries, the disease has ceased even to be mentioned by writers, such as Christie (1980), dealing with the general domain of infectious diseases. However, in African countries and India secondary syphilis remained a disease to be considered in the differential diagnosis of smallpox, up to the time of eradication. The roseolar and papular syphilitic rashes (Plate 1.29B) varied in size and distribution and felt different from those of smallpox. The individual lesions were sometimes hard, but they could not be rolled between the thumb and forefinger, to give the "shotty" feel characteristic of the smallpox vesicle. Neither could they be "split" by passing a needle horizontally through the lesion, as could the vesicles of smallpox. The

distribution was also different; if there were a profuse rash on the face, there would also be an equally dense rash on the chest and abdomen and the toxaemia would have been too slight for a case of smallpox with such a rash. Finally, the diagnosis would be clinched by the fact that the papules of syphilis did not evolve further, to vesicles and pustules, like those of smallpox.

Erythema multiforme

This disease (Plate 1.29C) could cause difficulties at any stage of the rash; the distribution of lesions is sometimes very like that of smallpox. In both diseases the patient could be quite ill and have a profuse vesicular eruption particularly affecting the extremities. However, the history is completely unlike that of smallpox: the onset of symptoms and rash tend to coincide and the rash evolves very rapidly to the vesicular stage. Further, erythema multiforme is almost always accompanied by stomatitis, and often by conjunctivitis and urethritis.

In severe cases there could be confusion with flat-type smallpox, since the vesicles were occasionally soft, superficial and flat, individually resembling those of flat-type smallpox. They sometimes coalesced and produced large bullae, also seen in some cases of severe smallpox. The degree of malaise was usually not like that seen in flat-type smallpox, where the patient at this stage had only about 48 hours to live, but the most important difference was in the speed of evolution of the rash in the two diseases. In smallpox with this skin picture the patient would have been ill and getting progressively worse for at least 10 days and the vesicular eruption would have only just fully emerged; in erythema multiforme the rash develops with the onset of constitutional symptoms and evolves rapidly to the vesicular stage.

Lesions due to vaccination

Generalized vaccinia, described in Chapter 7 (see Plate 7.7), rarely caused confusion; the history of vaccination and the nature and distribution of the rash differed substantially from what was found in smallpox. However, problems of precise diagnosis sometimes arose in smallpox contacts who had been vaccinated during what turned out to be the incubation period of smallpox. They usually showed a positive take at the vaccination site and often a modified rash, which could have been caused by variola or vaccinia virus. Operationally, all such cases were regarded as smallpox from the point of view of management. Precise diagnosis could be made by the culture of virus from several of the vesicles or pustules.

Drug eruptions

Although less important in countries in which smallpox was still endemic, drug eruptions (Plate 1.30A and B) were an important diagnostic problem in countries in which smallpox had been eradicated years before and doctors rarely considered the possibility of the disease. Many instances exist in which the rash of an imported case of smallpox, and sometimes the rashes of second generation cases deriving from it, were diagnosed as drug rashes, since the sick patients had customarily been treated with some kind of drug for the pre-eruptive fever. The diagnosis usually became quite clear with the passage of time and the evolution of the rash, but vaccine-modified smallpox could continue to mislead the physician if he had never considered smallpox as a possible diagnosis.

In endemic countries in recent years, since a wide variety of drugs have become available, cases of smallpox and drug eruption sometimes occurred coincidently. Rao (1972) described a case in which the drug rash completely obscured that due to smallpox and the diagnosis was only made when variola virus was recovered from some "seeds" extracted from the palms of the hands.

Rashes due to other causes

There are few diseases characterized by a rash that did not at some time suggest a diagnosis of smallpox, occasionally with dramatic effect in non-endemic countries. Acne, scabies and insect bites may be mentioned as examples. Coxsackievirus infections could pose a problem (Mukherjee et al., 1976), and in countries in which both diseases were endemic, dengue haemorrhagic fever and other arbovirus infections associated with a rash were sometimes initially diagnosed as smallpox.

Haemorrhagic-Type Smallpox

Haemorrhagic-type and flat-type smallpox were sometimes associated with a severe

Table 1.16. Alternative diagnoses in suspected but unconfirmed cases of smallpox

Final diagnosis	Series of cases		
	England and Wales, 1946–1948[a] (variola major)	India, 1976[b] (variola major)	Somalia, 1977–1979[c] (variola minor)
Chickenpox	41	53	20
Erythema multiforme	7	1	0
Allergic dermatitis	7	1	1
Drug rash	6	2	1
Syphilis	3	4	4
Impetigo	3	2	0
Scabies	1	1	0
Psoriasis	1	1	0
Vaccinia	5	0	1
Herpes	2	0	0
Measles	2	0	0
Rubella	1	0	0
Molluscum contagiosum	0	0	1
Septicaemia	4	0	0
Skin diseases (various)	14	5	0
Other (including no diagnosis made)	0	30	1
Total	97	100	29

[a] Modified from Conybeare (1950).
[b] During post-eradication surveillance in India (Basu et al., 1979).
[c] During post-eradication surveillance in Somalia (Ježek et al., 1981).

shock-like condition, loss of muscle tone and a peculiar state of apprehension and mental alertness that were said to be unlike the manifestations of any other infectious disease. The occurrence of a petechial rash, especially in the groin and along the flanks to the axillae, was regarded as diagnostic of smallpox, since other forms of febrile purpura, due to meningococci or other organisms, did not have such a localized and symmetrical distribution; but an accurate diagnosis was impossible without laboratory aid. The literature on outbreaks following the importation of smallpox into non-endemic countries (see Chapter 23) is replete with instances in which the index case or sometimes a first generation case, presenting as an acutely fatal case of haemorrhagic-type smallpox, was almost always misdiagnosed as meningococcal septicaemia (Plate 1.30C and D) or acute leukaemia. However, meningococcal bacteraemia is usually more rapidly lethal than was haemorrhagic-type smallpox; acute leukaemia is less rapid.

Erythematous rashes on the face and later on the arms and trunk sometimes suggested the diagnosis of toxic scarlet fever, but the early rash in haemorrhagic-type smallpox was a diffuse not a punctate erythema, the temperature was lower than in severe scarlet fever and the tongue and fauces were practically normal.

Even in endemic areas, and at times when variola major was a common disease, it was very difficult to diagnose very severe smallpox, whether of the haemorrhagic or of the flat type, in its early stages. It can be readily understood why the diagnosis was so often missed in non-endemic countries.

Effects of Prior Vaccination on Symptomatology

From the diagnostic point of view it was important for physicians to appreciate that there was great individual variation in the extent to which vaccinial immunity persisted. The person presenting with symptoms suggestive of flat-type smallpox, who had had a successful primary vaccination within 5 years, was unlikely to be suffering from this disease; the probability of another diagnosis should therefore have been seriously considered. On the other hand, the presence of signs or symptoms suggestive of a very mild attack of smallpox should not have led the doctor to discount the diagnosis even in the face of an apparently successful vaccination within a year. It was also important to remember that exceedingly mild smallpox, even variola sine eruptione, could occur in persons who had no evidence of ever having been successfully vaccinated.

Alternative Diagnoses

Several authors have summarized alternative diagnoses that have been made in suspected but unconfirmed cases of smallpox. Table 1.16 lists final diagnoses made in cases of suspected smallpox in situations in which variola major was the expected form of the disease (England and Wales, 1946–1948; India, 1976) and in those in which the endemic disease was variola minor (Somalia, 1977–1979). The overriding importance of chickenpox is apparent in all series. Marsden (1936) also reported that chickenpox was by far the commonest disease to be initially mistaken for variola minor in England (31% of 994 cases of suspected but unconfirmed smallpox). Other conditions suspected to be smallpox included almost all diseases that produced a rash.

LABORATORY CONFIRMATION OF SMALLPOX DIAGNOSIS

Laboratory methods played a crucial role in the global smallpox eradication programme; indeed, eradication could not have been confidently certified to have been achieved without their use. A detailed historical description of the laboratory methods used for the diagnosis of smallpox is presented in Chapter 2 and an account of the development of laboratory support for the Intensified Smallpox Eradication Programme is given in Chapter 10.

As well as being of critical importance in the global smallpox eradication programme, laboratory methods were also useful for the confirmation of clinical diagnoses. Indeed, although laboratory workers could make mistakes, the recovery of variola virus from a skin lesion was usually regarded as conclusive evidence that a particular patient was or had been suffering from smallpox. Such confirmation was rarely sought in endemic countries when smallpox was a common disease. Any doubtful case was always regarded as smallpox; containment and vaccination procedures operated independently of and were initiated before laboratory confirmation. However, laboratory confirmation or refutation of suspected smallpox was a valuable procedure in non-endemic countries and in smallpox-free regions of the endemic countries as eradication approached.

If an electron microscope was available, the examination of material from vesicles, pustules or scabs, examined by the negative staining technique, could give a rapid presumptive diagnosis of poxvirus, or sometimes herpesvirus, infection. Definitive diagnosis depended on the isolation of the causative virus on the chorioallantoic membrane of the developing chick embryo and its further characterization, if necessary, by biological tests. Usually the character of the pocks produced on the chorioallantoic membrane was distinctive enough for the diagnosis of variola, vaccinia, monkeypox or herpesvirus infection to be made (see Chapter 2).

In the period before the Intensified Smallpox Eradication Programme was launched, gel-precipitation tests were employed extensively in some national programmes (e.g., in India; Basu et al., 1979), and by laboratories that did not have an electron microscope. With adequate amounts of recently collected vesicle fluid it was an accurate and rapid test (World Health Organization, 1969a; A.W. Downie, personal communication, 1981), and when antivaricella serum was employed in parallel tests it could be used to differentiate smallpox from chickenpox (Brunell et al., 1971; A.R. Rao, personal communication, 1981).

TREATMENT: PROPHYLACTIC AND CURATIVE

No disease better illustrated the adage "Prevention is better than cure" than smallpox. Nevertheless, until 1975 millions of persons were infected with variola major virus and, as the foregoing description of its clinical features bears witness, it was a horrible disease with a high case-fatality rate. Any treatment that would ameliorate the severity of the disease in those who were infected would have been welcomed.

In this section, treatment administered after exposure and thus during the incubation period is called "prophylactic" and treatment given after the development of symptoms "curative". Three procedures were used or investigated: vaccination after exposure, immunoprophylaxis and immunotherapy, and chemoprophylaxis and chemotherapy.

Vaccination during the Incubation Period

The sheet anchor of smallpox control during the Intensified Smallpox Eradication

Programme was surveillance and containment (see Chapter 10). Containment was possible because vaccination provided protection against infection for those who had not already been infected with variola virus. However, vaccination must also be discussed as a form of prophylactic treatment, for it also modified the progress of the disease in persons vaccinated during the first few days of the incubation period. The precedent for this concept was Pasteur's demonstration of protection against rabies by vaccination during the incubation period. The different timescales of the pathogenesis of vaccinia and variola (see Fig. 1.3 and Fig. 3.1 of Chapter 3) provided hope that such prophylactic treatment, if carried out during the first week of the incubation period of smallpox, might ameliorate or sometimes abort the disease. Precise data were difficult to obtain, because it was rarely known whether or when a contact had actually been infected with variola virus. Unless sophisticated serological tests had been carried out (and this was never done) it would have been impossible to differentiate between a person sustaining only vaccination and one who had also been incubating smallpox but in whom that infection had produced no symptoms. However, all observers agree that persons in whom smallpox developed a week or more after primary vaccination often had a modified attack. Dixon (1962) summarized his review of the older literature by saying that "at least 50% of cases where successful primary vaccination had occurred during the first week [of the incubation period] will get some vaccine-modification and reduction of severity, whereas when done at a later period the number showing such modification is not likely to be over 20%". In fact, on theoretical grounds the degree of modification might be expected to be highly dependent on the exact timing of infection with variola virus and vaccination; the more nearly these corresponded, the greater was the degree of protection. Without distinguishing the timing of primary vaccination, Rao (1972) observed a frequency of modified-type smallpox of 8.8% among those given primary vaccination after exposure, compared with 1.0% among unvaccinated patients.

Successful revaccination would have been expected to be even more effective, because of the accelerated immune response.

Immunoprophylaxis and Immunotherapy

Although the procedure was rendered superfluous by the development of effective measles vaccines, measles could be aborted or ameliorated by the administration of immune gamma-globulin during the first 7 days of the incubation period (Janeway, 1944). During the 1960s some experimental work was carried out in animals (see Chapter 3), and a few trials were made in human beings, to determine whether immunoprophylaxis or immunotherapy might be useful in smallpox.

The most comprehensive trials were carried out in Madras (Kempe et al., 1956, 1961). Immune gamma-globulin, prepared from the serum of recently vaccinated adults (not smallpox convalescents) was administered to close contacts of smallpox cases, most of whom were also vaccinated or revaccinated at the same time. The results of these and other trials (Marennikova, 1962), summarized in Table 1.17, indicate that if given during the incubation period vaccinia-immune gamma-globulin provided protection additional to that expected from vaccination at that time. The greater potency against variola virus of homologous antiserum from smallpox convalescents (Downie & McCarthy, 1958; Downie et al., 1961b) might have been expected to give even better results, but no trials were ever made with such sera. In any case vaccinia-immune or variola-immune gamma-globulin were available in such small quantities that they could only have been used in unusual situations. However, vaccinia-immune gamma-globulin did appear to have a place in the prevention and treatment of vaccination

Table 1.17. Seroprophylaxis of smallpox: effects of vaccinia-immune gamma-globulin on the occurrence and severity of smallpox in vaccinated case contacts

Reference	No antiserum			Received antiserum		
	Number	Cases	Deaths	Number	Cases	Deaths
Kempe et al. (1956)	75	8	3	56	2	1
Kempe et al. (1961)	379	21	0	326	5	0
Marennikova (1962)	29	13	..[a]	13	0	—

[a] Not stated; probably zero.

complications in some especially susceptible individuals (see Chapters 7 and 11).

Chemoprophylaxis and Chemotherapy

It is not surprising that orthopoxviruses, being the largest and most complex viruses, were among the first for which antiviral agents were developed that were effective in inhibiting viral replication in cells (see Chapter 2). Some of these drugs also had activity against orthopoxvirus infections in mice and they were subsequently tested for the treatment and chemoprophylaxis of smallpox. The results were disappointing, in that none was effective in treatment, and chemoprophylaxis was of marginal value only and did not compare in effectiveness with the vaccination of contacts.

Thiosemicarbazones for chemotherapy

The effectiveness of certain thiosemicarbazones in the treatment of tuberculosis led to the demonstration by Hamre et al. (1950) that some thiosemicarbazones reduced the mortality of mice inoculated with vaccinia virus. This led to the testing by pharmaceutical companies of many different thiosemicarbazones, two of which (*N*-methylisatin *β*-thiosemicarbazone (metisazone (methisazone)) and 4-bromo-3-methylisothiazole-5-carboxaldehyde thiosemicarbazone (M & B 7714)) appeared to be particularly effective against variola in mice (Bauer & Sadler, 1960; Rao et al., 1965). Clinical trials for the treatment and prophylaxis of smallpox were carried out in Madras (see reviews by Bauer (1972) and Rao (1972)).

Both drugs were only slightly soluble and were given as tablets or as a micronized preparation in syrup. The main side-effects were nausea and vomiting, which were sometimes severe. Rao et al. (1966a, 1969b) carried out double-blind trials of both thiosemicarbazones (Table 1.18). The only apparent differences between the treated and control groups were small reductions in the already low case-fatality rates in vaccinated subjects. However analysed, there were no significant differences in case-fatality rates between the unvaccinated treated subjects and the controls; nor were there any significant differences in symptomatology among the small number of cases of ordinary-type smallpox whom it was possible to treat as early as the 5th day of disease (2nd day of rash).

Thiosemicarbazones for chemoprophylaxis

Clearly, these thiosemicarbazones were useless for the treatment of smallpox. However, Bauer et al. (1963) had claimed impressive results in chemoprophylaxis with metisazone in a trial in Madras. Most of the case contacts had been vaccinated during infancy and again shortly after detection of the index cases. Among 1100 subjects treated with metisazone there were 3 cases of smallpox and no deaths. Of 1126 controls not given the drug, 78 developed smallpox and 12 died. The result was hailed enthusiastically: "...if further experience of this substance leads to equally favourable conclusions, the work...will perhaps rank as the most significant advance

Table 1.18. Case-fatality rates in patients treated with either of two thiosemicarbazones and placebos[a]

Group	Clinical type									
	Flat		Ordinary			Modified		Total		
	Cases	Deaths	Cases	Deaths	Case-fatality rate (%)	Cases	Deaths	Cases	Deaths	Case-fatality rate (%)
Unvaccinated:										
Metisazone[b]	4	3	121	39	32.2	1	0	126	42	33.3
Control	3	3	116	31	26.7	2	0	121	34	28.1
M & B 7714[c]	51	48	373	102	27.3	8	0	432	150	34.7
Control	33	33	345	99	28.7	5	0	383	132	34.5
Vaccinated:										
Metisazone[b]	2	2	69	1	1.4	11	0	82	3	3.7
Control	0	0	75	6	8.0	19	0	94	6	6.4
M & B 7714[c]	7	3	172	2	1.2	69	0	260	5	1.9
Control	5	5	144	3	2.1	81	0	218	8	3.7

[a] Based on Rao et al. (1966a, 1969b).
[b] Metisazone = *N*-methylisatin *β*-thiosemicarbazone.
[c] M & B 7714 = 4-bromo-3-methylisothiazole-5-carboxaldehyde thiosemicarbazone.

A Comment on Chemoprophylaxis in Smallpox

"The major drawback to routine use of the drug [metisazone] is the frequency of often severe nausea and vomiting which occurs in not less than 25% and more often in two-thirds or more. In presently endemic countries, use of the drug is wholly impractical, not only in terms of acceptance on the part of the population, but because of the logistics involved in giving it. It has been difficult enough to persuade health administrators of the need for immediate investigation and control of all outbreaks and even more difficult to establish the mechanics for doing this properly. Use of methisazone would require not only administration of the drug but repeat visits to determine whether vomiting had occurred and, if necessary, repeat administration of the drug. This cannot be considered.

"In the non-endemic developed countries, one could more easily cope with the logistics of administration. It is noted, however, that vaccinia immune globulin has been shown to have a protective efficacy of the same order of magnitude as methisazone but without the associated toxic side effects." (D.A. Henderson, unpublished report, December 1970.)

in smallpox control since the days of Jenner" (*Lancet*, 1963). Such a comment was perhaps pardonable in Great Britain at a time when there were rather frequent importations of variola major from the Indian subcontinent. Statements in the Indian press, such as "at last a drug has come to replace the much dreaded vaccination" (quoted by Rao, 1972), were more serious in their implications for the control and eradication of smallpox.

There were major defects in the design of this trial: treatment and control groups were not allocated at random, contacts were not visited daily, and assessment of the taking of the drug (which caused nausea and vomiting) was made by questioning at a second visit 2 weeks after supplies of it had been distributed. Further trials with metisazone gave variable but mostly favourable results, which are summarized in Table 1.19. Rao et al. (1966b) reported a less favourable but still significant result with unvaccinated contacts given M & B 7714 as a chemoprophylactic drug.

The overall conclusion is that, given prophylactically, metisazone did exert some protective effect, but its administration was often associated with severe nausea and vomiting. Health administrators considered its use in countries in which smallpox was still endemic in the late 1960s and early 1970s as "wholly impractical" (see box) in terms of acceptability by the populations concerned and the logistics of administering it. In non-endemic countries these difficulties would be less serious but in these situations vaccinia-immune globulin, which had a protective effect of the same magnitude as metisazone, without toxic side-effects, was available. Prompt vaccination or revaccination of contacts remained the sheet anchor of prophylaxis until smallpox was finally eradicated.

Cytosine arabinoside

In an uncontrolled trial in Bangladesh, Hossain et al. (1972) reported promising

Table 1.19. Summary of results of thiosemicarbazone prophylaxis in smallpox

Reference[a]	Variety of smallpox	Treated group			Controls		
		Number	Cases	Deaths	Number	Cases	Deaths
Bauer et al. (1963)	Variola major[b]	1 101	3	0	1 126[c]	78	12
Bauer et al. (1969)[d]	Variola major[b]	2 292	6	2	2 560[c]	102	18
Rao et al. (1969a)	Variola major[b]	17	2	1	20[e]	8	2
Heiner et al. (1971c)	Variola major[b]	262	7	1	260[e]	13	2
Valle et al. (1965)	Variola minor[f]	187	7	0	219[c]	38	0
Rao et al. (1966b)	Variola major[g]	196	40	7	201[e]	60	12

[a] Metisazone was used in all the studies except those of Rao et al. (1966b), who used M & B 7714.
[b] All subjects vaccinated after exposure.
[c] No placebo drug given.
[d] Includes data published in Bauer et al. (1963).
[e] Received placebo.
[f] Unvaccinated subjects.
[g] All subjects unvaccinated until after chemoprophylaxis had begun.

results with cytosine arabinoside in the treatment of variola major. However, subsequent controlled studies in both variola major (Monsur et al., 1975) and variola minor (Dennis et al., 1974) provided no evidence of any effect on either the mortality (in variola major) or the clinical progression of the disease. Nor was the related drug, adenine arabinoside, of any use (Koplan et al., 1975).

Symptomatic Treatment

In the absence of any effective therapy for established cases of smallpox, treatment was symptomatic and demanded above all good nursing care, which put great demands on the devotion and skill of the nursing staff. In the crowded smallpox hospitals in endemic countries most nursing care was in fact provided by members of the patient's family, who often came to stay in the hospital.

In endemic countries, in which hospital facilities were often poor, patients were usually better looked after at home in their village surroundings. Koplan et al. (1978) showed that the case-fatality rate was substantially higher in hospitals than in village surroundings, mainly because only the more severe cases, often in persons without local family support, were admitted to hospital, and devoted family care was better than the nursing provided in grossly overcrowded hospitals. Another reason for encouraging treatment at home during the Intensified Smallpox Eradication Programme was the frequency with which smallpox was transmitted to other patients in hospitals, which often left much to be desired in terms of their overall administration and management of other patients, visitors and staff.

CHAPTER 2

VARIOLA VIRUS AND OTHER ORTHOPOXVIRUSES

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INTRODUCTION

Because of its distinctive clinical picture, described in the previous chapter, smallpox has been recognized as a disease entity for many centuries. Its control by deliberate intervention, at first by variolation, then by vaccination, began long before such measures were adopted for any other disease. Likewise, knowledge of the virus that produced the disease and those that were used to control it, variola and cowpox or vaccinia viruses respectively, is as old as the relatively new science of virology. The particles that cause these two diseases were seen with the microscope, and then by electron microscopy, before any other viruses had been visualized, and their chemical composition was analysed earlier than that of any other animal virus. The family to which they belong, now called Poxviridae, was correctly categorized before any other viral family, and the genus *Orthopoxvirus*, whose members are the causative agents of smallpox, vaccinia and the several related diseases with which this book is less directly concerned, was delineated as early as any other viral genus as the "variola-vaccinia subgroup" of the poxvirus group.

This chapter outlines the historical development and current state of knowledge of the orthopoxviruses, based primarily on studies with vaccinia virus. Much of the material presented will be of special interest to biologists, but it includes topics of greater complexity and of a more technical nature than can be readily understood by the otherwise informed general reader. However, the authors consider that it is important in this book to endeavour to embrace the full scope of currently available knowledge of the orthopoxviruses. For the virologist the account will appear unbalanced, since the intention is to limit it to providing the virological background that is necessary to understand how the body responds to infection with these viruses, how the clinical diagnosis can be confirmed by laboratory studies, and what other related agents may pose threats to man,

The Nature of Viruses in General and Poxviruses in Particular

Viruses form a distinct group of agents, which differ fundamentally from cellular microorganisms. The infective particle, known as the virion, is inert; it proceeds to a dynamic phase only after it enters a susceptible cell and loses enough of its outer protective layers to allow its genetic material to be transcribed and translated. The inert poxvirion is the largest of all virions and its genetic material, a single molecule of double-stranded DNA, is among the largest of all viral genomes. Poxviruses differ from most other DNA viruses in that they replicate in the cytoplasm rather than in the nucleus of susceptible cells. To accomplish this, they have a battery of enzymes not found in other DNA viruses, including a viral DNA-dependent RNA polymerase which transcribes messenger RNA from the viral DNA.

confuse the diagnosis or give rise to problems in interpreting ecological data. To do this it will be necessary to describe some features of the orthopoxviruses, such as their structure, the composition of their genetic material and their behaviour in experimental animals, in some detail, but it is not necessary to provide a detailed analysis of the complex events of the replication cycle, a feature which has always been of central interest to virologists.

CLASSIFICATION AND NOMENCLATURE

The internationally accepted classification of viruses is based primarily on the morphology of the viral particle (virion) and the nature and structure of the viral nucleic acid. As the largest of all viruses, the virions of poxviruses were the first to be seen with the microscope.

Development of Knowledge of the Structure of Poxvirions

As early as 1886, Buist (see Gordon, 1937) reported that he had seen what must have been the virions of vaccinia virus in stained smears, although he regarded them as spores. Calmette & Guérin (1901) used the rabbit to assay batches of vaccine lymph and in the course of this work they observed that the lymph contained numerous minute refractile particles which they suggested might be the "virulent elements". These observations were confirmed by Prowazek (1905), an expert microscopist, who found that they could be stained by Giemsa's method, and revived the term "elementary bodies", originally introduced by Chaveau (1868) and used until recently to describe the virions. Paschen (1906) used a modified Loeffler's flagellar stain and championed the belief that the elementary bodies of vaccinia virus thus made visible with the microscope were the infective particles; they were later also called "Paschen bodies" in recognition of Paschen's extensive work in this field (Plate 2.1). Negri (1906) had shown that the infectivity of vaccine lymph would remain after the lymph had been passed through a filter that held back bacteria, but final proof that the elementary body was indeed the infectious entity was not provided until Ledingham (1931) showed that antisera produced against vaccinia or fowlpox viruses would simultaneously and specifically agglutinate the particles and neutralize the infectivity of the homologous but not the heterologous virus.

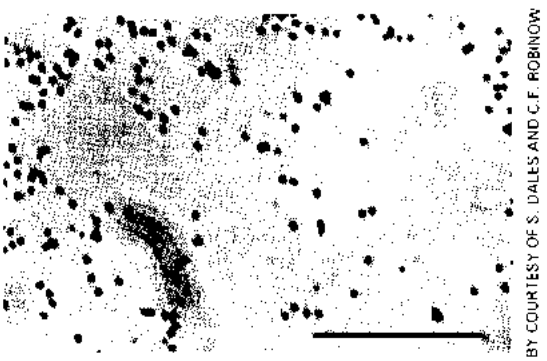

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Plate 2.1. "Elementary bodies" (virions) of vaccinia virus. Bar = 1 μm. Imprint of a rabbit cornea infected with vaccinia virus, prepared and stained by Paschen in 1906.

Further analysis of the structure of pox virions has depended on the use of the electron microscope with virions treated in various ways. Enzymatic digestion was used to demonstrate the existence of a substructure within the brick-shaped virions (Dawson & McFarlane, 1948). In a series of classical studies, Peters (1956), using enzymatic digestion with deoxyribonuclease and metal shadowing, demonstrated the major viral components and designated them as the outer membrane, the lateral bodies and the core. Thin sections of infected cells have been particularly valuable in elucidating the morphogenesis of the virions of vaccinia virus. Negative staining, combined with a variety of methods of degrading the virion, has been useful in analysing the substructure of vaccinia virions (Easterbrook, 1966; Medzon & Bauer, 1970) and in demonstrating the distinctive surface structure of the outer membrane. The negative staining method, first used for poxviruses by Nagington & Horne (1962), was the cornerstone of the laboratory diagnosis of smallpox as it was developed during the Intensified Smallpox Eradication Programme.

The Nucleic Acid of Poxviruses

Following the development of methods of purification of vaccinia virus by differential centrifugation, workers at the Rockefeller Institute of Medical Research in New York showed that the virions contained 5.6% DNA (Hoagland et al., 1940) but no RNA (Smadel & Hoagland, 1942). The DNA was shown to be double-stranded, with a guanine + cytosine content of 36–37% (Joklik, 1962), and subsequent studies showed that it occurred as a single linear molecule with a relative molecular mass of about 123 million comprising 186 000 base pairs (186 kbp).

Classification of Poxviruses

Traditional classifications of diseases were based on symptoms, and certain diseases of man, cow, horse, sheep and pig were grouped together as "poxes" because they were characterized by pocks on the skin. Several of these diseases were caused by poxviruses, but the deficiencies of a classification of causative agents based on signs and symptoms were highlighted by the inclusion of chickenpox (caused by a herpesvirus) and "the great pox" (syphilis—caused by a spirochaete) in the same category as smallpox.

By examining sections of poxvirus-infected tissues, pathologists came to recognize cytoplasmic inclusion bodies as characteristic of poxvirus infection (Guarnieri, 1892), although for many years they were regarded as protozoa. Gradually, however, the significance of the minute particles seen in stained smears was appreciated, and by the 1920s Aragão (1927) grouped together, as belonging to one family, the viruses of "myxoma, smallpox, molluscum contagiosum, epithelioma of fowls, etc.". Subsequently, Goodpasture (1933) formally proposed that vaccinia-variola, fowlpox, horsepox, sheep-pox, goat-pox, swinepox and molluscum contagiosum viruses should be grouped together as the genus *Borreliota*. Some years later, Buddingh (1953), using particle morphology and the character of the inclusion bodies as well as symptomatology and host range as the criteria, suggested a classification which, as far as it goes, accords with current ideas, except that all viruses with mammalian hosts were included in the same subgroup.

Writing on behalf of the Poxvirus Subcommittee set up by the Sixth International Congress for Microbiology, Fenner & Burnet (1957) produced a short description of the poxvirus group that has remained the basis of subsequent classifications in respect of the criteria used and the subdivisions adopted, although the names they proposed for species were not accepted, and the status of categories (genus, species, etc.) has been changed. With a view to bringing order and international agreement into viral classification and nomenclature, an International Committee on Nomenclature of Viruses was established in 1966, at the Ninth International Congress for Microbiology in Moscow. This Committee, whose name was subsequently changed to the International Committee on Taxonomy of Viruses, is now accepted as the international adjudicator on viral taxonomy and nomenclature (Matthews, 1983); the currently accepted classification of the poxviruses of vertebrates is set out in Table 2.1.

Chordopoxvirinae: the Poxviruses of Vertebrates

The basic features of members of the subfamily Chordopoxvirinae are the large size

Table 2.1. The classification of poxviruses of vertebrates

Family	Poxviridae	
Subfamily	Chordopoxvirinae	
Genera	*Orthopoxvirus*	(vaccinia)
(prototype species)	*Avipoxvirus*	(fowlpox)
	Capripoxvirus	(sheep-pox)
	Leporipoxvirus	(myxoma)
	Parapoxvirus	(milker's nodule)
	Suipoxvirus	(swinepox)
	Unclassified	molluscum contagiosum, tanapox

and characteristic ovoid or brick-like shape of the virion and the possession of a genome consisting of a single linear molecule of double-stranded DNA with a relative molecular mass that ranges, for different genera, between 85 million for *Parapoxvirus* and 185 million for *Avipoxvirus*. The virions of all members incorporate several enzymes, including a DNA-dependent RNA polymerase. These enable poxviruses to replicate in the cytoplasm of infected cells.

The Genus *Orthopoxvirus*

The subfamily Chordopoxvirinae includes many viruses that are related to each other only in the general properties just listed. The genus with which this chapter is concerned, *Orthopoxvirus*, is much more homogeneous, as befits its lower taxonomic status. Table 2.2 lists the names, host ranges and geographical distribution of what, on the basis of their biological properties and genome structure, are 9 distinct species of *Orthopoxvirus*. All these species show extensive serological cross-reactivity, by both *in vitro* tests (gel diffusion, complement fixation, haemagglutination inhibition, etc.) and by neutralization tests and cross-protection in laboratory animals; indeed the last two tests form the basis for the tentative allocation of a poxvirus isolate to the genus *Orthopoxvirus*.

Traditionally (e.g., Baxby, 1975, 1977b), species of *Orthopoxvirus* have been named primarily on the basis of the host animal from which they were derived, and identified on the basis of a range of biological characteristics in laboratory animals. The most important indicators were the host range, the morphology of the pock and the ceiling temperature at which it was produced on the chorioallantoic membrane of the developing chick embryo. The situation was changed by the discovery by Müller et al. (1978) and Esposito et al. (1978) that the DNAs of representative strains of each of several different species of *Orthopoxvirus* showed distinctive patterns after digestion with restriction endonucleases. With a larger number of strains of several different species, Mackett & Archard (1979) showed that all species of *Orthopoxvirus* shared a large conserved central part of their genomes. Analysis of the DNA structure now provides an alternative and more fundamental primary criterion for the classification of orthopoxviruses (see Fig. 2.6).

Recognized Species of *Orthopoxvirus*

Historical features relating to the discovery and recognition of the accepted species of *Orthopoxvirus* are summarized below.

Variola virus

This virus, which caused human smallpox, has a restricted host range in laboratory

Table 2.2. Species of the genus *Orthopoxvirus*

Species	Animals found naturally infected	Host range in laboratory animals	Geographical range: natural infections
Variola	Man (infection now eradicated)	Narrow	Formerly world-wide
Vaccinia	Numerous: man, cow,[a] buffalo,[a] pig,[a] rabbit[a]	Broad	World-wide
Cowpox	Numerous: cow, man, rats, cats, gerbils, large felines, elephants, rhinoceroses, okapis	Broad	Europe (and Turkmenian SSR)
Monkeypox	Numerous: monkeys, great apes, anteaters, squirrels, man	Broad	Western and central Africa
Ectromelia	Mice, ?voles	Narrow	Europe
Camelpox	Camels	Narrow	Africa and Asia
Taterapox	*Tatera kempi* (a gerbil)	Narrow	Western Africa
Raccoonpox	Raccoons	?Broad	USA
Uasin Gishu disease	Horses (from a wildlife reservoir host)	Medium	Eastern Africa

[a] Infected from man.

animals. Early reports of its transfer to animals are difficult to interpret, but monkeys were used quite early (Zuelzer, 1874) and extensively (e.g., Brinckerhoff & Tyzzer, 1906). Variola virus was subsequently grown in the rabbit cornea and a test developed to differentiate it from chickenpox virus (Paul, 1915). Later it was grown in chick embryos (Torres & Teixeira, 1935), and North et al. (1944) and Downie & Dumbell (1947b) showed that the pocks produced by variola virus on the chorioallantoic membrane were sufficiently distinctive to allow its differentiation from vaccinia and cowpox viruses. A detailed account of the virology of variola virus is presented later in this chapter.

Vaccinia virus

Though a different species of *Orthopoxvirus* from Jenner's "variolae vaccinae", vaccinia virus is the agent that has been most widely used for vaccination. Baxby (1977c, 1981) has summarized speculations about its origins (see Chapter 7). Many strains are supposed to have been derived from variola virus (Wokatsch, 1972; see Chapter 11). However, when experiments were carried out under conditions which precluded the possibility of cross-infection with vaccinia virus, "transformation" of variola virus into vaccinia virus could not be demonstrated (Herrlich et al., 1963).

There are many strains of vaccinia virus with different biological properties, although all have many features in common, such as their wide host range, rapid growth on the chorioallantoic membrane and distinctive genome maps. Since vaccinia virus has a broad host range and has been very widely used for many decades, accidental infections of domestic animals were not uncommon when human vaccination was practised on a large scale (see Table 2.7). Sometimes serial transmission occurs naturally in such animals (cows, buffaloes, rabbits).

In the history of smallpox eradication, vaccinia virus is second only to variola virus in its importance. It is also the "model" orthopoxvirus, with which the vast majority of laboratory investigations of viruses of this genus have been performed. Aspects of its virology are further discussed later in this chapter and its use in the prevention of smallpox is described at length in Chapters 6, 7 and 11.

Cowpox virus

For many years before the time of Jenner, cowpox had been recognized as a disease of cows that was transmissible to man, producing ulcers on the cow's teats and on the milker's hands. The distinction between cowpox and vaccinia viruses was first made by Downie (Davies et al., 1938; Downie, 1939a,b). A number of strains of *Orthopoxvirus* recovered from diverse animals in zoos and circuses, as well as from rodents (see Chapter 29), have now been recognized as being very similar in both their biological properties and their genome maps to the strains of cowpox virus that have been recovered from cows and man; all of these strains belong to the cowpox virus species. Since cowpox virus was so important in the history of smallpox control (see Chapter 6) and causes occasional infections in man (see Chapter 29), its properties are discussed at greater length later in this chapter.

Monkeypox virus

This virus was first recovered from cynomolgus monkeys that had been captured in Malaysia in 1958 and shipped by air to Copenhagen, where they were housed together for several weeks before the disease was recognized (Magnus et al., 1959; see Chapter 29). Several other isolations of the virus were subsequently made from captive primates in Europe and North America between 1960 and 1968 (Arita & Henderson, 1968). In 1970 monkeypox virus was isolated from a case of a disease in a human being in Zaire diagnosed clinically as smallpox (Ladnyj et al., 1972; Marennikova et al., 1972a); human monkeypox has now been recognized as a rare zoonosis occurring in several countries in western and central Africa.

Monkeypox virus infection in monkeys has been used as a model for the study of the pathogenesis of smallpox (see Chapter 3). The properties of monkeypox virus, the clinical and epidemiological features of human monkeypox, and its ecology in Africa are discussed in Chapter 29.

Ectromelia virus

Infectious ectromelia, later called mousepox, was described in the United Kingdom by Marchal (1930), and the virus was subsequently recovered from laboratory mice in

many parts of the world (Fenner, 1982). Serological studies (Kaplan et al., 1980) suggest that voles may be a reservoir host of ectromelia virus in nature. Mousepox has been extensively used as a model system for studies relevant to the pathogenesis and immunology of smallpox (see Chapter 3). Ectromelia virus does not produce disease in man (Fenner, 1949a).

Camelpox virus

This virus shares several biological properties with variola virus and was originally described as being "extremely closely related" to variola virus (Baxby, 1972). However, it behaves differently in cultured cells (Baxby, 1974) and has a distinctive genome structure (Fig. 2.6). The camel appears to be the only natural host. It was first isolated in tissue culture by Ramyar & Hessami (1972) and its affinities with the genus *Orthopoxvirus* were recognized by Baxby (1972). Extensive studies in Somalia during the Intensified Smallpox Eradication Programme confirmed that it did not cause disease in man (Ježek et al., 1983).

Taterapox virus

This virus was recovered from pooled liver/spleen material obtained from small naked-soled gerbils (*Tatera kempi*) captured in Benin in 1964 (Kemp et al., 1974). It was studied by Gispen (1972) and Huq (1972), and characterized as a species of *Orthopoxvirus* by Lourie et al. (1975), who described it as "like variola minor virus" and speculated about its possible role in the long-term survival of variola virus. However, it has a distinctive genome map (see Fig. 2.6), which shows the usual features of orthopoxvirus DNA.

Nothing is known of its natural history, and little except what is shown in Table 2.3 is known of its biological properties. Taterapox virus may be one of several orthopoxviruses responsible for the high proportion of positive results obtained in orthopoxvirus haemagglutination-inhibition tests carried out on sera derived from a variety of wild animals captured in tropical rain forest regions in Africa (see Chapter 29).

Raccoonpox virus

The only indigenous orthopoxvirus yet recovered from the Americas, this virus was isolated from raccoons in the eastern USA (Alexander et al., 1972) and characterized as a distinct species of *Orthopoxvirus* by Thomas et al. (1975). Its genome could not be mapped by methods used for other orthopoxviruses, since only about half the *Hin*dIII restriction endonuclease fragments cross-hybridized with those of other orthopoxviruses (Esposito & Knight, 1985), indicating a much more distant relationship than that found between other orthopoxviruses.

Uasin Gishu disease virus

This is an African orthopoxvirus recognized only by the fact that it causes papular lesions in horses in parts of Kenya (Kaminjolo et al., 1974a,b). It appears to be a virus enzootic in African wildlife, and if more widely distributed it could complicate ecological studies of monkeypox virus by blurring the serological picture.

CHARACTERISTICS SHARED BY ALL SPECIES OF *ORTHOPOXVIRUS*

Having shown the way in which early studies of the morphology of poxvirus particles led to a classification of the family and the designation of the genus *Orthopoxvirus*, it is necessary now to outline current views on the structure and chemistry of these viruses. The vast majority of such studies were carried out with vaccinia virus, but they apply, with minor variations, to all orthopoxviruses.

Morphology of the Virion

Fig. 2.1, which is based on electron microscopic studies of vaccinia virus using thin sections, negative staining and freeze-etching, represents the virion as consisting of four major elements: core, lateral bodies, outer membrane and, as an inconstant component, an envelope. The well-defined central core (Plate 2.2C and D) contains the viral DNA, and on each side of the core there is an oval mass called the lateral body. The core and lateral bodies are enclosed within a well-defined "outer membrane", which has a characteristic ribbed surface structure (Plate 2.2A and Fig. 2.1), and is composed of a large number of surface tubules (Plate 2.3). The viral DNA within the core, which is associ-

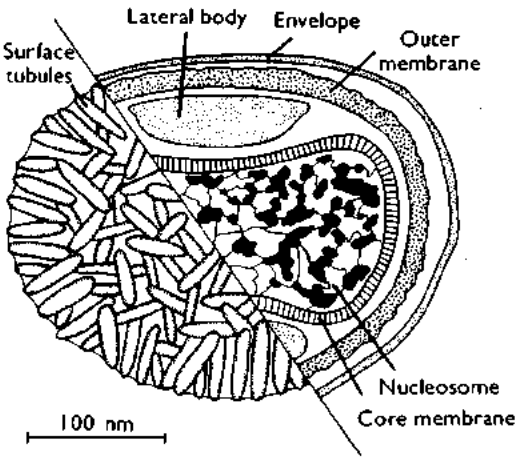


Fig. 2.1. The structure of the vaccinia virion. Right-hand side, section of enveloped virion; left-hand side, surface structure of non-enveloped particle. The viral DNA and several proteins within the core are organized as a "nucleosome". The core has a 9-nm thick membrane, with a regular subunit structure. Within the virion, the core assumes a dumb-bell shape because of the large lateral bodies. The core and lateral bodies are enclosed in a protein shell about 12 nm thick—the outer membrane, the surface of which consists of irregularly arranged tubules, which in turn consist of small globular subunits. Virions released naturally from the cell are enclosed within an envelope which contains host cell lipids and several virus-specified polypeptides, including the haemagglutinin; they are infectious. Most virions remain cell-associated and are released by cellular disruption. These particles lack an envelope so that the outer membrane constitutes their surface; they also are infectious.

ated with at least 4 different proteins, is maintained in a superhelical configuration, and appears to occur in globular structures interconnected by DNA-protein fibres, resembling the nucleosome structures of eukaryotic chromatin (Soloski & Holowczak, 1981). Virions released spontaneously from cells are often enclosed within a lipoprotein envelope (Plate 2.2B) which contains the vaccinia haemagglutinin and several other virus-specific polypeptides (Payne & Norrby, 1976; Payne, 1978). Virions released by cellular disruption are infectious but lack an envelope (Appleyard et al., 1971); their outer surface is then composed of the outer membrane.

The envelope probably plays a role in the spread of virions within the animal body and thus in pathogenesis (see Chapter 3). More important in the context of smallpox control is the suggestion that the low protective power of inactivated vaccines (see Chapters 3 and 11) is due in part to the fact that they consist of inactivated non-enveloped virions (Boulter & Appleyard, 1973), whereas live virus vaccines produce envelope proteins in the process of replication.

Antigenic Structure

The large and complex virions of orthopoxviruses contain a very large number of polypeptides, each of which probably contains several epitopes (antigenic sites). Much modern virological research is concerned with the structure and function of the viral polypeptides, their location in the virion and the processes by which they are produced during viral replication. Such research will undoubtedly illuminate our understanding of the biology of orthopoxviruses and the way in which they cause disease, but it is peripheral to the practical problems with which this book is concerned. However, three aspects of the composition of these polypeptides and their antigenic makeup are highly relevant: (1) some antigens show cross-reactivity across the whole subfamily Chordopoxvirinae; (2) many antigens, including those important in generating a protective immune response, show cross-reactivity within the genus *Orthopoxvirus*; and (3) some antigens are species-specific.

Antigens common to the subfamily Chordopoxvirinae

Investigations carried out some years ago using crude chemical and serological methods showed that one or several antigens were shared by all members of the subfamily that could be studied. Takahashi et al. (1959) demonstrated that both myxoma-immune sera and vaccinia-immune sera reacted with members of the *Orthopoxvirus*, *Leporipoxvirus*, and *Avipoxvirus* genera when tested by complement-fixation and immunofluorescence tests. Woodroofe & Fenner (1962) were able to demonstrate group cross-reactivity by complement-fixation or immunofluorescence tests only when they extracted the so-called "NP antigen" (Smadel et al., 1942) from myxoma or vaccinia virus. Such preparations reacted with antisera to a wide range of poxviruses, belonging to 5 different genera.

Ikuta et al. (1979) reinvestigated the problem, using radioimmunoprecipitation, and

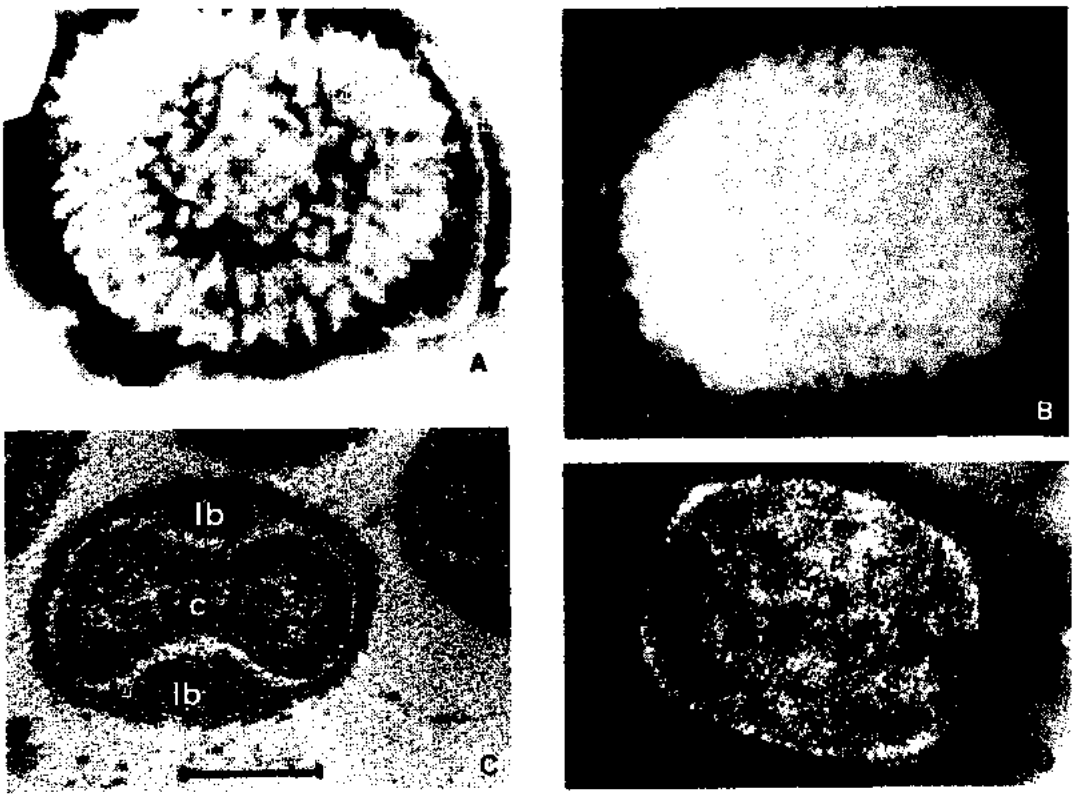


Plate 2.2. Electron micrographs of vaccinia virions. **A**: Non-enveloped virion, showing the surface tubular elements that make up the outer membrane. **B**: Enveloped virion, as released from the infected cell and found in extracellular medium. **C**: Thin section of non-enveloped virion showing the biconcave core (c) and the two lateral bodies (lb). **D**: Viral core, released after treatment of virions with Nonidet 40 and mercaptoethanol. Bar = 100 nm. (**A** from Dales, 1963; **B** from Payne & Kristensson, 1979; **C** from Pogo & Dales, 1969; **D** from Easterbrook, 1966.)

demonstrated that among the 30 antigenic polypeptides found in one-dimensional gels prepared from cells infected with vaccinia, cowpox and Shope fibroma viruses (the last-named belonging to the genus *Leporipoxvirus*) there were 4 which showed cross-reactivity between the orthopoxviruses and Shope fibroma virus. There were, as expected, additional cross-reactive polypeptides shared by vaccinia and cowpox viruses but not found in fibroma virus.

These subfamily serological cross-reactions are not without practical importance. If methods that detect many different antigen–antibody reactions are used in serological surveys of animal sera for evidence of orthopoxvirus infection (e.g., immunofluorescence, enzyme-linked immunosorbent assay (ELISA), or radioimmunoassay), positive reactions may be produced by agents other than orthopoxviruses, such as tanapox virus, i.e., a positive result may mean only that the donor of the serum has been infected with a member of the subfamily Chordopoxvirinae.

Cross-reactions between orthopoxviruses

An unknown agent having been identified as a poxvirus, perhaps by electron microscopy of infected tissues (see, for example, the work of Kaminjolo et al. (1974a) with the virus of Uasin Gishu disease), the next step in its identification as an orthopoxvirus depends on various kinds of serological cross-reactions between it and a recognized member of the genus, such as vaccinia virus. Three kinds of reactions are employed: (1) cross-protection in laboratory animals or cross-neutralization of infectivity; (2) demonstration of an orthopoxvirus-specific haemagglutinin; and (3) analysis of soluble antigens in agar gels by precipitation in gel, immunoelectrophoresis or radioimmunoprecipitation reactions. Both cross-protection and cross-neutralization are

strictly genus-specific, and orthopoxviruses are the only members of the family Poxviridae that produce a haemagglutinin.

Cross-protection. This is the classical way of demonstrating the relatedness of poxviruses as members of the same genus. It was first performed as a deliberate experiment by Jenner (1798), when he inoculated James Phipps with pus from a case of smallpox—2 months after having inoculated him with cowpox virus obtained from Sarah Nelmes. Cross-protection remains the most important test for membership of the genus *Orthopoxvirus*; it can now be supplemented by comparisons of DNA maps.

Cross-neutralization of infectivity. Cross-protection tests depend on a range of immune reactions, cell-mediated as well as humoral. A more limited but more flexible test, since it can be performed in eggs or cultured cells, is the neutralization of infectivity of the homologous and selected heterologous viruses by convalescent serum. This test has been widely used for demonstrating the relatedness of various orthopoxviruses (e.g., Downie & McCarthy, 1950; McNeill, 1968).

"Protective antigens"—i.e., those which elicit the production of neutralizing antibodies to orthopoxviruses—fall into two classes: the surface tubular elements of the outer membrane of the virion and some of the virus-specific antigens in the viral envelope. A protein with a relative molecular mass of 58 000 polymerizes to form the surface tubules that are a prominent feature of the outer membrane of vaccinia virions (Plate 2.2A). These surface tubular elements have been isolated from virions in a pure form (Plate 2.3); they elicit neutralizing antibody to non-enveloped but not to enveloped virions and block the neutralizing capacity of antibody to non-enveloped virions (Stern & Dales, 1976; Payne, 1980).

Other protective antigens are located in the viral envelope, which is found only in virions that are released naturally from cells. Analysis of the differences between the polypeptides of non-enveloped virions and enveloped virions by one-dimensional polyacrylamide gel electrophoresis (Payne, 1978) showed that the envelope contained 10 additional polypeptides (9 of which were glycosylated) with relative molecular masses of between 20 000 and 210 000.

Antibody to the isolated envelopes neutralized the infectivity of enveloped forms of vaccinia virus, as demonstrated by the "anti-comet" test of Appleyard et al. (1971) (see Chapter 3, Plate 3.10), whereas antibody to inactivated non-enveloped virions did not do so (Payne, 1980). It is not known which of the envelope polypeptides are involved in neutralization reactions.

Haemagglutination-inhibition tests. Of all the poxviruses, only those of the genus *Orthopoxvirus* produce a haemagglutinin. This is active only on certain kinds of chicken cells (Nagler, 1942) and, with ectromelia virus, on mouse cells (Mills & Pratt, 1980). The agglutinability of chicken cells is genetically determined; White Leghorns produce agglutinable red blood cells whereas several other strains of chicken (e.g., Plymouth Rock) do not (Suzuki et al., 1955). It was the detection of haemagglutination that could be inhibited by vaccinia-immune serum that led Burnet & Boake (1946) to suggest that ectromelia virus was a member of the genus *Orthopoxvirus*. More recently, the production of the characteristic haemagglutination has been important in suggesting that raccoonpox virus (Thomas et al., 1975), taterapox virus (Lourie et al., 1975) and the virus of Uasin Gishu disease (Kaminjolo et al., 1974b) belong to this genus.

Early studies showed that vaccinia haemagglutinin was a lipoprotein, composed of a viral antigen and a lipid which was responsible for attachment to the red blood cell (Burnet, 1946; Stone, 1946; Chu, 1948). Active haemagglutinin can be reconstituted from these two components after they have been separated by ether/ethanol extraction (Smith et al., 1973). From the time of its discovery, the haemagglutinin was regarded as separable from the virus particle (Burnet & Stone, 1946) and this was the orthodox view for many years. However, the numerous investigations that demonstrated the dissociation of haemagglutinin and virion were carried out with preparations obtained by the disruption of infected cells. With the demonstration that vaccinia virions were sometimes released in an enveloped form, the problem was reinvestigated by Payne & Norrby (1976) and Payne (1979), who demonstrated that vaccinia haemagglutinin is the dominant glycoprotein in the envelopes of vaccinia virions and also occurs in the membranes of cells infected with vaccinia virus, where it can be demonstrated by haemadsorption tests. When cells are disrupted, the non-enveloped virions are readily separable from the haemagglutinin by centrifugation.

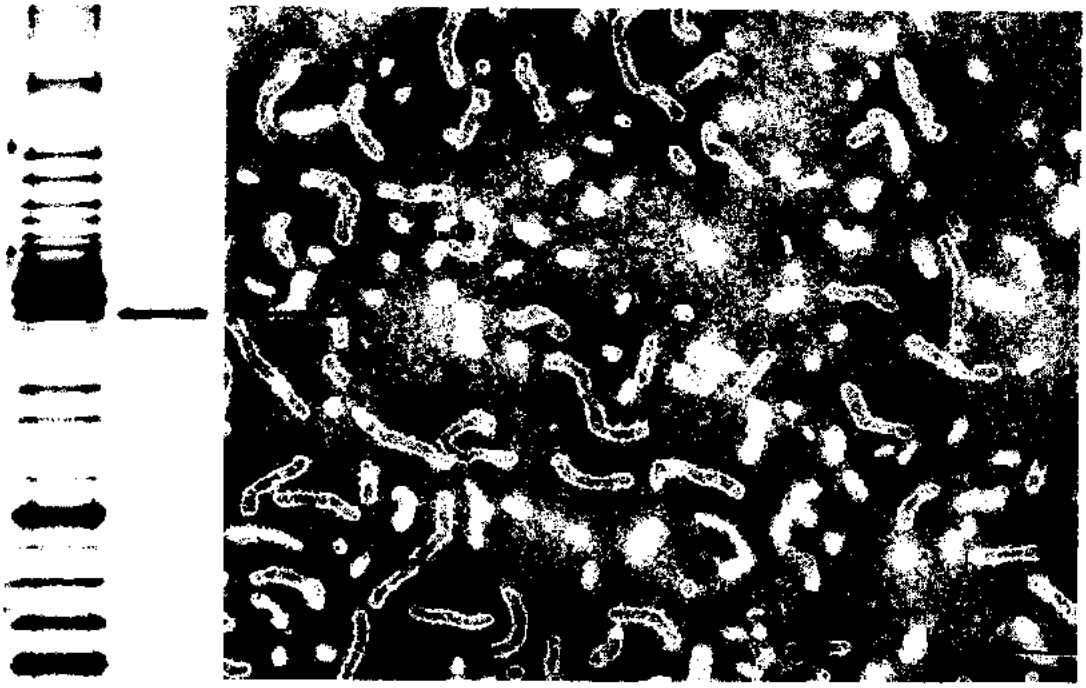


Plate 2.3. Purified surface tubules of the outer membrane of vaccinia virus. Bar = 100 nm. On the left is the upper part of an electropherogram of virion polypeptides run side by side with a preparation of the surface tubules that migrates as a single band of 58 K. (From Stern & Dales, 1976.)

Haemagglutinins of different species of *Orthopoxvirus* cross-react extensively. Using sera from immunized chickens, McCarthy & Helbert (1960) found no evidence of specificity for homologous antigens. On the other hand, Fenner (1949a) found that homologous titres were always higher than heterologous, when comparing vaccinia and ectromelia haemagglutinins. Infection with ectromelia virus of mice previously vaccinated with vaccinia virus resulted in a reversal of titres of inhibition of the respective haemagglutinins.

Analysis of soluble antigens. As already described, there are a few soluble antigens that show cross-reactivity throughout the subfamily Chordopoxvirinae. However, there are very many more that show cross-reactivity within each genus. The principal uses of methods of identifying soluble antigens (gel diffusion and radioimmunoprecipitation) are twofold: (1) in analysing the dynamics of viral replication and the detailed structure of the orthopoxvirion; and (2) in comparing different mutants, strains and species of *Orthopoxvirus*. In the present context, demonstration of extensive cross-reactivity between a known orthopoxvirus and a new poxvirus isolate would provide strong evidence that the latter belonged to this genus.

Composition and Structure of the Viral DNA

The genome of all members of the genus *Orthopoxvirus* is a single linear molecule of double-stranded DNA, with relative molecular masses varying for different species from 110 million to 140 million, comprising between 165 kbp and 210 kbp. Orthopoxvirus DNAs contain no unusual bases and the guanine + cytosine content is very low—about 36%. The relative molecular mass of the DNA of different strains of vaccinia virus varies between 118 million and 125 million.

Vaccinia virus DNA behaves in an anomalous way when it is denatured. Instead of separating, the two sister strands form a large single-stranded circular molecule, being attached at or near each end of the genome by covalent links (Geshelin & Berns, 1974). For the most part the DNA sequences in the vaccinia genome are unique, but the two terminal fragments cross-hybridize with each other (Wittek et al., 1977) and with the termini of other species of orthopoxvirus (Mackett & Archard, 1979). This inverted terminal repetition is about 10 kbp long in the strains of vaccinia virus used by Wittek, but

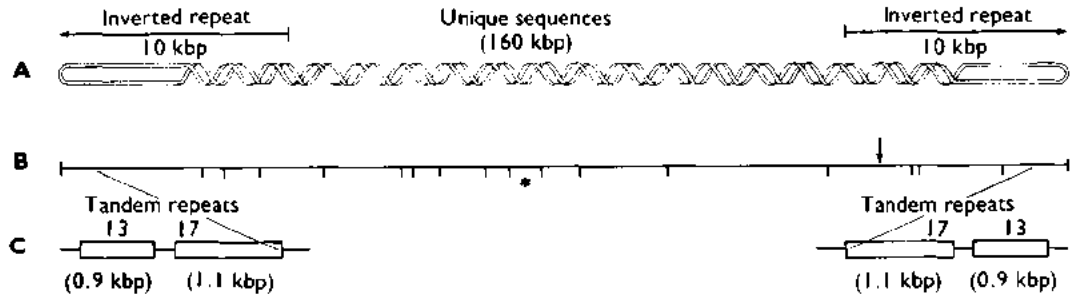


Fig. 2.2. Schematic representation of the DNA of vaccinia virus (Lister strain). **A**: Linear double-stranded molecule with terminal hairpins and inverted repeats (not to scale). When denatured it forms a very large single-stranded circular molecule. **B**: Cleavage sites of restriction endonucleases *Hin*dIII (vertical lines) and *Sma*I (arrow). The asterisk indicates the fragment containing the thymidine kinase gene, which is used in experiments with vaccinia virus as a vector for hybrid vaccines. **C**: Each 10 kilobase pair (kbp) terminal portion includes 2 groups of tandem repeats of short sequences rich in adenine–thymidine.

its length varies considerably in other orthopoxviruses. For example, in a series of mutants of cowpox virus studied by Archard et al. (1984), the length of the terminal repetition varied from 4.5 kbp to 41 kbp, almost 20% of the entire genome. Within each terminal repeat of vaccinia virus there are 30 reiterations of a 70-bp sequence arranged in tandem and grouped into 2 discrete groups of 17 and 13 units (Wittek & Moss, 1980; Fig. 2.2). Garon et al. (1978) visualized the terminal repetition by electron microscopy, which showed that the opposite ends of each strand are complementary to each other. The continuity of the DNA chain around the single-strand hairpin loop at the end of the molecule was shown in a variety of ways, culminating in the determination of the base sequence by Baroudy et al. (1982).

The analysis of vaccinia DNA and of the differences between DNAs derived from different species, strains and mutants of orthopoxviruses entered a new phase with Wittek's determination of a physical map of vaccinia virus DNA by analysis of the fragments produced when it was treated with various restriction endonucleases (Wittek et al., 1977).

Restriction endonuclease analysis provides a most important tool for the study of orthopoxviruses. On the one hand it opened the way to the cloning of selected fragments of orthopoxvirus DNA in *Escherichia coli*, ultimately encompassing the whole of the viral DNA, with all its implications for the examination of the molecular biology of viral replication. On the other hand, the demonstration by Mackett & Archard (1979) that a large central part of the genome of all orthopoxviruses is very similar makes restriction endonuclease analysis a powerful method for taxonomic comparisons of different orthopoxviruses. In this book the composition of the DNA, as determined by restriction endonuclease analysis, has been accepted as the ultimate criterion for allocating viruses to species within the genus *Orthopoxvirus*, and as the technique of choice for examining the affinities of various strains and mutants that have been recovered from time to time.

Non-genetic Reactivation

Poxviruses exhibit a unique kind of reactivation of "killed" virus. It was first observed by Berry & Dedrick (1936) with the leporipoxviruses myxoma virus and fibroma virus and was called viral "transformation". However, it is now known to be a general property of the poxviruses of vertebrates. Poxviruses that have been inactivated by methods which do not damage their DNA can be reactivated; any active member of the subfamily Chordopoxvirinae appears to be able to reactivate any other member of that subfamily inactivated by, for example, heating (review: Fenner, 1962). Reactivation depends on single cells being co-infected with the two viruses concerned, and is essentially an example of complementation. Heating destroys the core-associated DNA-dependent RNA polymerase; the active virus provides this enzyme, or enzymes that release DNA from the cores of both the active and the reactivated viruses. Non-genetic reactivation is a useful tool for obtaining hybrids between orthopoxviruses.

Restriction Endonuclease Mapping of Orthopoxvirus DNAs

Restriction endonucleases are bacterial enzymes that cleave double-stranded DNA at sites which are determined by sequences of 4 or 6 nucleotides. To compare the DNAs of different orthopoxviruses, a few enzymes have been selected for which there are only a few cleavage sites along the whole length of the viral genome. After digestion, the mixture of DNA fragments is separated by electrophoresis in agarose gels, stained and photographed to show the bands of DNA arranged in accordance with their molecular weights. Cross-hybridization with selected radioactively labelled fragments of other orthopoxvirus DNAs makes it possible to identify relationships between different orthopoxviruses and arrange the fragments in a linear order along the viral genome (see Fig. 2.6).

To simplify comparisons between the maps of different orthopoxvirus species, strains and mutants, a method of computer-aided analysis of the cleavage sites described by Gibbs & Fenner (1984) has been used. Briefly, the maps of different DNAs are aligned along selected highly conserved cleavage sites. All other cleavage sites for particular enzymes, on all the DNAs under study, are then compared and scored as present, absent, or "impossible" (the DNA molecule may be too small to accommodate the cleavage site in question). The figures thus obtained are analysed by the computer program MULCLAS (Lance & Williams, 1967) and the results expressed as a dendrogram indicating degrees of dissimilarity. The absolute values depend on the number of attributes (separate cleavage sites) in the group of DNAs under study, so that different dendrograms may give quite different figures for the "index of dissimilarity" between the same DNA molecules, if different restriction enzymes or groups of enzymes are used. With orthopoxvirus DNAs such analysis may place undue weight on the effects of internal deletions and transpositions, but it offers a rough method of comparing strains that is better than visual comparisons of the DNA maps (see Fig. 2.7).

More detailed analysis of the orthopoxvirus DNA is carried out by incorporating selected fragments into plasmids and then into *Escherichia coli*. Large quantities of the selected fragments can then be produced and analysed by further digestion with restriction endonucleases for which there are numerous cleavage sites, or particular pieces of DNA can be sequenced.

CHARACTERIZATION OF ORTHOPOXVIRUSES BY BIOLOGICAL TESTS

Morphology is useful for classification only at the subfamily level, since only the genus *Parapoxvirus* can be unequivocally distinguished from the other genera of Chordopoxvirinae by the morphology of the virions, as seen in negatively stained preparations. Cross-protection and neutralization tests make it possible to allocate a poxvirus to the genus *Orthopoxvirus*. Allocation of an orthopoxvirus to a particular species depends on the use of several biological and chemical tests, respectively to categorize the effects of the virus in various animals and cell systems and to define the nature of its DNA and polypeptides.

In this book attention will be concentrated on the attributes of the 4 orthopoxviruses that were of most significance in relation to smallpox and its eradication: variola, vaccinia, cowpox and monkeypox viruses. More detailed descriptions of the biology of these viruses, and that of the other species of *Orthopoxvirus*, can be found in Fenner et al. (1987).

Lesions in Rabbit Skin

Historically, one of the earliest tests which clearly differentiated variola from vaccinia virus was the demonstration that only the latter virus produced lesions in rabbit skin, after either scarification or intradermal inoculation. Subsequent investigations have confirmed the value of this test.

Within the *Orthopoxvirus* genus, there is a correlation between the reaction in rabbit skin (Plate 2.6) and the character of the pocks produced on the chorioallantoic (CA) mem-

c. 1955

Plate 2.4. Allan Watt Downie (b. 1901). Formerly Professor of Bacteriology in the University of Liverpool, Downie was a leading worker in the virology and immunology of poxviruses from the late 1930s until the 1970s and made major contributions to our knowledge of cowpox, variola and tanapox viruses. K.R. Dumbell (Plate 2.12) and H.S. Bedson (Plate 2.14) trained under him as graduate students.

brane (see below). Each of 3 species (cowpox, monkeypox and neurovaccinia, including rabbitpox virus) which produce haemorrhagic (ulcerated) pocks on the CA membrane cause large indurated skin lesions with a purple-coloured central area that usually ulcerates before healing. "Dermal" strains of vaccinia virus, which produce small white pocks on the CA membrane, and white pock mutants of cowpox, monkeypox and rabbitpox viruses elicit smaller, pink, nodular lesions. Variola, camelpox and ectromelia viruses produce at most a small papule with transient erythema, which is non-transmissible.

Pocks on the Chorioallantoic Membrane

All orthopoxviruses produce pocks on the CA membrane, without the need for adaptation by passage. Goodpasture et al. (1932) first cultivated vaccinia virus on the CA membrane and Keogh (1936) demonstrated that dermal and neurotropic strains of vaccinia virus produced readily distinguishable kinds of pocks, which were white and haemorrhagic (ulcerated) respectively. In contrast, variola virus produces small white pocks on the CA membrane, which can be readily distinguished from those of vaccinia virus (North et al., 1944). Cowpox virus was first cultivated on the CA membrane by Downie (1939a), who showed that it produced bright-red haemorrhagic pocks, clearly distinguishable from those of both vaccinia and variola viruses (Plate 2.5).

Monkeypox virus was not recognized until 1958, when Magnus et al. (1959) demonstrated pocks, which "resembled closely those described for variola virus", on CA membranes inoculated with material from pustular lesions on infected monkeys. Later studies (Marennikova et al., 1971; Rondle & Sayeed, 1972) showed that the pocks of monkeypox virus are distinguishable from those of other orthopoxviruses; like those of variola virus, they are small, but instead of being dense, white and opaque, they are pink and have an ulcerated, slightly haemorrhagic surface.

The pocks produced by species that elicit opaque white pocks on the CA membrane are usually uniform in character; all pocks on a membrane are similar. On the other hand, species or strains of virus that produce ulcerated pocks (cowpox, monkeypox, and the neurovaccinia and rabbitpox strains of vaccinia virus) regularly produce white pock mutants (Downie & Haddock, 1952; Fenner, 1958; Gemmell & Fenner, 1960; Dumbell & Archard, 1980), which usually differ from the strains producing red pocks in several other biological characteristics, such as the type of lesion in the rabbit skin and, often, their lethality for mice and chick embryos. Vaccinia virus passaged for commercial vaccine production may contain virions producing both white and grey ulcerated pocks; the passage of vaccinia virus by intracerebral or intratesticular inoculation of rabbits or mice usually selects for mutants which produce ulcerated, haemorrhagic pocks on the CA membrane.

Ceiling Temperature

When carrying out experiments on the growth of several different viruses on the CA membrane, Burnet (1936) noticed that ectromelia virus produced pocks at 37 °C but not at 39.5 °C. This finding was developed by Bedson & Dumbell (1961), who introduced the concept of the "ceiling temperature" as the highest temperature at which pock formation on the CA membrane would occur. The ceiling temperature has proved to be a useful criterion for distinguishing between different species of *Orthopoxvirus* (Table 2.3). It has also

Appearance of Orthopoxvirus Pocks on the Chorioallantoic Membrane

The most useful laboratory test for distinguishing between species of *Orthopoxvirus* is the appearance of pocks on the CA membrane. Unlike plaques in cultured cells, which result from the direct interaction between cells and virus, a third component enters into the appearance of pocks—namely, leukocytes and erythrocytes delivered to the site via the bloodstream. Basically, a pock is a greyish-white focus, varying in diameter from 0.4 mm to 4 mm, according to virus species. It is produced by a combination of hyperplasia of the ectodermal layer of the CA membrane and the infiltration of cells into the mesodermal layer. Sometimes, as with variola virus, the surface of the pock is glossy white, owing to pronounced hyperplasia of the ectoderm; sometimes, as with monkeypox virus, the superficial layer ulcerates and there is a superficial haemorrhage into the crater. The pocks of cowpox virus are bright red, because very little leukocytic infiltration occurs and there are capillary haemorrhages into the pock.

Expression of the "characteristic" pock phenotype is influenced by the concentration of pocks and the temperature of incubation. Expression of the "red" pock phenotype is enhanced when the pocks are semiconfluent or confluent. Also, at higher temperatures pocks tend to be greyish-white and non-ulcerated, whereas at lower temperatures some species (but not variola virus) produce pocks with an ulcerated, haemorrhagic centre. For example, at 37 °C camelpox virus produces small pocks very similar to those of variola virus (Mayr et al., 1972), but at 35 °C it produces pocks with a haemorrhagic centre (Marennikova et al., 1973). Likewise, at 37 °C monkeypox virus produces white pocks very like those of variola virus (Magnus et al., 1959), whereas at 35 °C the pocks are ulcerated and haemorrhagic (Marennikova et al., 1971).

proved useful in distinguishing between variola major and alastrim viruses (Nizamuddin & Dumbell, 1961; Dumbell & Huq, 1986). Cultured cells can also be used for measuring ceiling temperatures (Porterfield & Allison, 1960).

Different species of orthopoxviruses recovered from geographically separate places and at different times usually have the ceiling temperature characteristic of the species. However, in the laboratory ceiling temperature mutants, which are then usually called temperature-sensitive (*ts*) mutants, can be readily obtained by appropriate selection methods. Sambrook et al. (1966) and Dales et al. (1978) have recovered large numbers of different *ts* mutants of vaccinia virus. Conversely, Dumbell et al. (1967) obtained two thermo-efficient strains of variola major virus by serial passage at incrementally higher temperatures.

Lethality for Mice and Chick Embryos

The response to infection depends on the age of the animal and its genetic background, the route of inoculation, and the viral species or strain. Variola virus is much less lethal for mice and chick embryos than the other species of *Orthopoxvirus* that can infect man (Table 2.3).

Growth in Cultured Cells

Most orthopoxviruses can be grown in one or another kind of cultured cell and assayed by plaque counts in suitable susceptible cells. Species which have a wide host range among intact animals (e.g., vaccinia, cowpox and monkeypox viruses) tend to grow to high titres and in a wide range of cells, and to produce lytic plaques. Species with a restricted host range, such as variola virus, replicate in a narrower range of cells and often produce hyperplastic foci (see Plate 2.13). However, on serial passage, adaptation occurs readily and may involve change to a more lytic plaque. Monolayers infected with viruses that produce hyperplastic foci usually yield much less virus than those infected with viruses that produce lytic plaques, since most cells in the monolayer remain uninfected. Differential growth capacity in particular cell lines (e.g., the rabbit cell line RK 13 and pig embryo

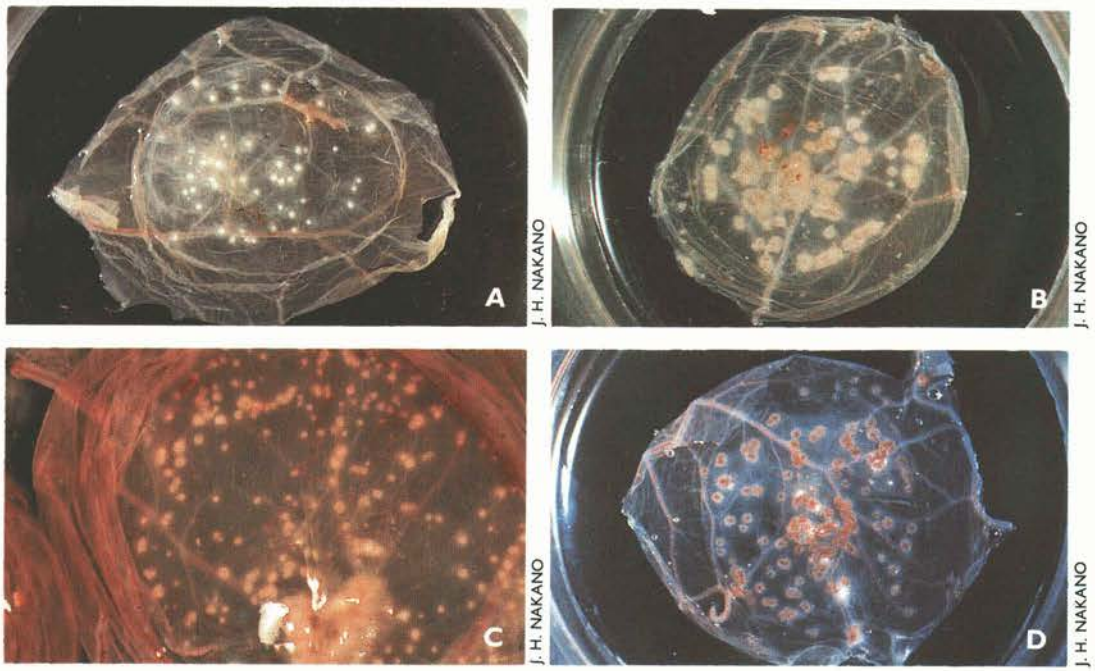


Plate 2.5. The appearance of pocks on the chorioallantoic membrane produced by various species of *Orthopoxvirus* that infect man. Monkeypox virus pocks photographed after incubation for 3 days at 35 °C; all others after 3 days at 36 °C. **A:** Variola major virus. **B:** Vaccinia virus (Lister strain). **C:** Monkeypox virus (Copenhagen strain). **D:** Cowpox virus (Brighton strain).

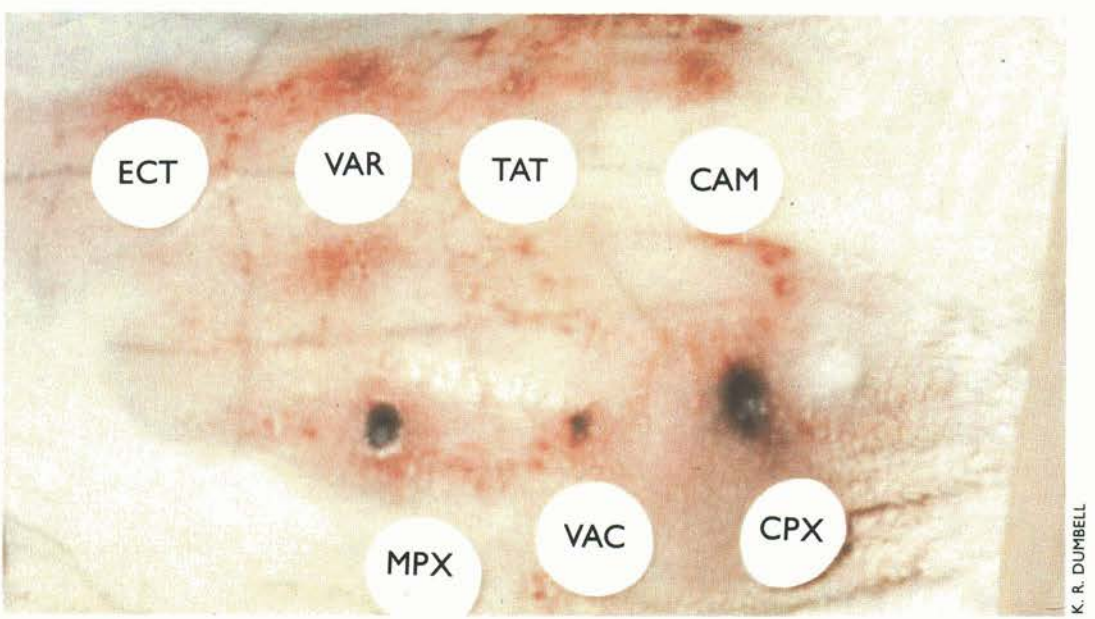
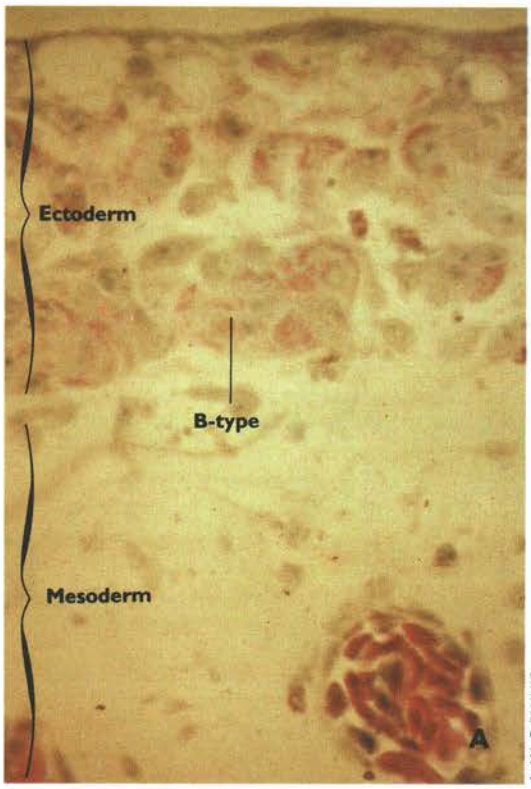


Plate 2.6. Lesions produced in the rabbit skin 5 days after the intradermal inoculation of doses of 10^5 pock-forming units of various species of *Orthopoxvirus*. Ectromelia (ECT), taterapox (TAT) and camelpox (CAM) viruses produce no lesions and variola (VAR) virus elicits only a slight erythema. Monkeypox (MPX) and cowpox (CPX) viruses produce large indurated lesions with a purple centre that often ulcerates. The response to vaccinia virus (VAC) varies with the strain; "dermal" strains usually produce a distinct red indurated nodule and neurovaccinia a lesion like that produced by cowpox virus.



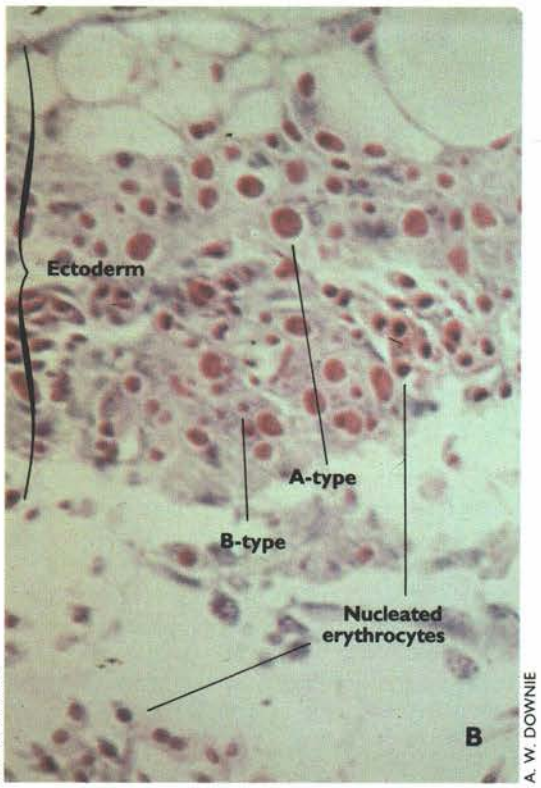
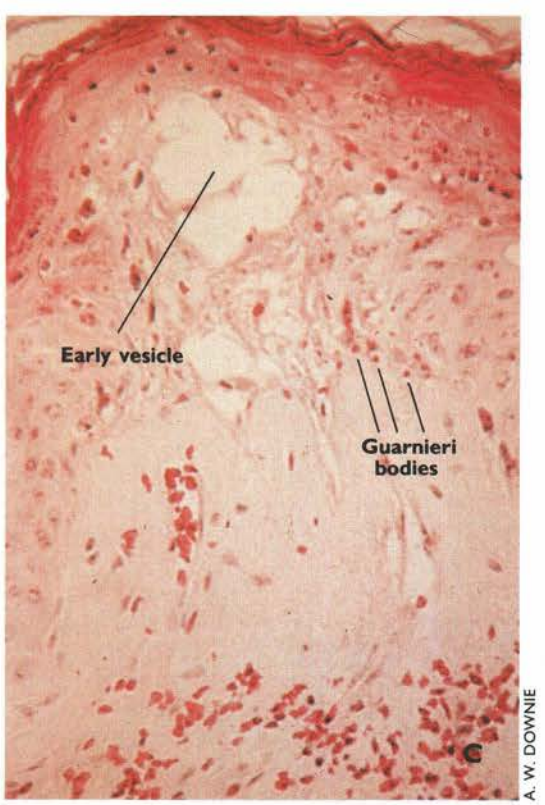


Plate 2.7. Cytoplasmic inclusion bodies in cells infected with orthopoxviruses. **A:** B-type inclusion bodies (Guarnieri bodies) in hyperplastic ectodermal cells of the chorioallantoic membrane, in a pock produced by variola virus. Note that the surface of the pock is intact and there are no erythrocytes in the ectoderm, although they are present within a vessel in the mesoderm. (Eosin and methyl blue stain.) **B:** B-type (pale-red, irregular) and A-type (large eosinophilic, with halo) inclusion bodies in ectodermal cells of the chorioallantoic membrane, in a pock produced by cowpox virus. There are also a number of nucleated erythrocytes in the ectoderm and free in the mesoderm, and the surface of the pock is ulcerated. **C:** Section of the skin of a patient with haemorrhagic-type smallpox, showing Guarnieri bodies, and free erythrocytes below an early vesicle. (Haematoxylin and eosin.)



kidney cells) may be useful in distinguishing between variola and monkeypox viruses when these viruses are first inoculated into such cells (see below); however, adaptation occurs readily.

Since the viral haemagglutinin is inserted into the cytoplasmic membrane of infected cells, haemadsorption can be used to detect orthopoxvirus infection in cultured cells. Different patterns of haemadsorption have proved useful in distinguishing between isolates of variola virus from different parts of the world (see below).

Inclusion Bodies

Two kinds of inclusion bodies occur in the cytoplasm of cells infected with orthopoxviruses, which Japanese investigators (Kato et al., 1959) have distinguished as A-type and B-type (Plate 2.7). B-type inclusions are the sites of viral replication and are produced by all orthopoxviruses. A-type inclusions are strongly eosinophilic and are found only in cells infected with cowpox, ectromelia and raccoonpox viruses.

Comparison of Biological Characteristics of Different Species

Although a good deal of variation in biological behaviour occurs between different strains of the orthopoxviruses that have been the most carefully studied, certain characteristics appear to be regularly associated with each species (Table 2.3). Most of the characteristics listed are usually or invariably found with recently isolated strains of all species; some appear to be very stable, whereas others can be altered by the deliberate selection of mutants or by serial passage at high concentration.

VIRAL REPLICATION

Viral replication is a central focus of virology, yet it is largely peripheral to the understanding of smallpox and vaccination, with which this book is concerned. We shall therefore restrict the description of the replication of poxviruses to a simplified diagram (Fig. 2.3), and describe briefly aspects that are relevant to the pathogenesis and immunology of smallpox and vaccinia—namely, the initiation of infection, assembly and release of progeny virions and changes in infected cells. The reader interested in a more detailed account of poxvirus replication should consult Moss (1985) or Fenner et al. (1987).

Adsorption, Penetration and Uncoating

The first stage of viral infection consists of adsorption to and penetration of host cells. Enveloped and "naked" orthopoxvirus particles, although both infectious, behave differently. The outer membrane of the non-enveloped particle fuses with the plasma membrane at the surface of the cell, or within a vacuole formed by invagination of the plasma membrane, thus releasing the viral core into the cytoplasm. Enveloped virions are adsorbed more rapidly and efficiently, which explains why they play an important role in the spread of infection, both in cultured cells and in intact animals (see Chapter 3).

Assembly and Maturation

Electron microscopic analysis of thin sections of infected cells suggest a sequence of developmental events, shown diagrammatically in Fig. 2.4. The initial stages of virion formation occur in circumscribed granular electron-dense areas of the cytoplasm. The first morphologically distinct structures are crescents (or cupules in three dimensions) consisting of a bilayer membrane with a brush-like border of spicules on the convex surface and granular material adjacent to the concave surface (Plate 2.8). The spicules are thought to give the membrane its rigid convex shape, which determines the size of the immature viral particles. Ultimately the spicules appear to be replaced by the surface tubular elements of the outer membrane. The immature viral membranes appear circular (or spherical in three dimensions) with a dense nucleoprotein mass embedded in a granular matrix. The nucleoprotein appears to enter the immature envelopes just before they are completely sealed. It is unclear whether the majority of the proteins destined to form the mature particle, which includes proteins of the core membrane and the lateral bodies and many viral enzymes, are enclosed within the membrane of the immature particle or injected simultaneously or sequentially after its

Table 2.3. Biological characteristics of recognized species of *Orthopoxvirus*

Characteristic	Variola virus	Vaccinia virus	Cowpox virus	Monkeypox virus	Ectromelia virus	Camelpox virus	Taterapox virus	Raccoonpox virus	Uasbin Gishu poxvirus
Pocks on CA membrane[a]	Small opaque white	Strains vary; large opaque white or ulcerated	Large haemorrhagic	Small opaque ulcerated	Very small opaque white	Small opaque white	Small opaque white	Very small opaque white	Medium size, opaque white
Ceiling temperature (CA membrane)	37.5–38.5 °C	41 °C	40 °C	39 °C	39 °C	38.5 °C	38 °C	?	?
Rabbit skin lesion	Erythema and papule, non-transmissible	Strains vary; indurated nodule, sometimes haemorrhagic	Indurated, haemorrhagic	Indurated, haemorrhagic	Erythema and papule, non-transmissible	Erythema and papule, non-transmissible	Small papule, non-transmissible	Very small nodule	No lesion
Disease in Asian monkeys	Generalized rash	Large lesion, localized	Large lesion, localized	Generalized rash	?	Large lesion, localized	Susceptible, no rash	?	?
Lethality for:									
Suckling mice	Low	Strains vary; high to very high	Variable	High	Very high	Low	Low	High	Pocks on skin of baby mice
Chick embryos	Low	High	Medium	Medium	Medium	Low	Low	?	?
Type-A inclusion bodies	–	–	+	–	+	–	–	+	–
Thymidine kinase sensitivity[b]	+	–	–	–	–	–	–	?	?

[a] Chorioallantoic membrane: examined at 48 hours for vaccinia virus and at 72 hours for all others.
[b] Sensitivity to inhibition by thymidine triphosphate.

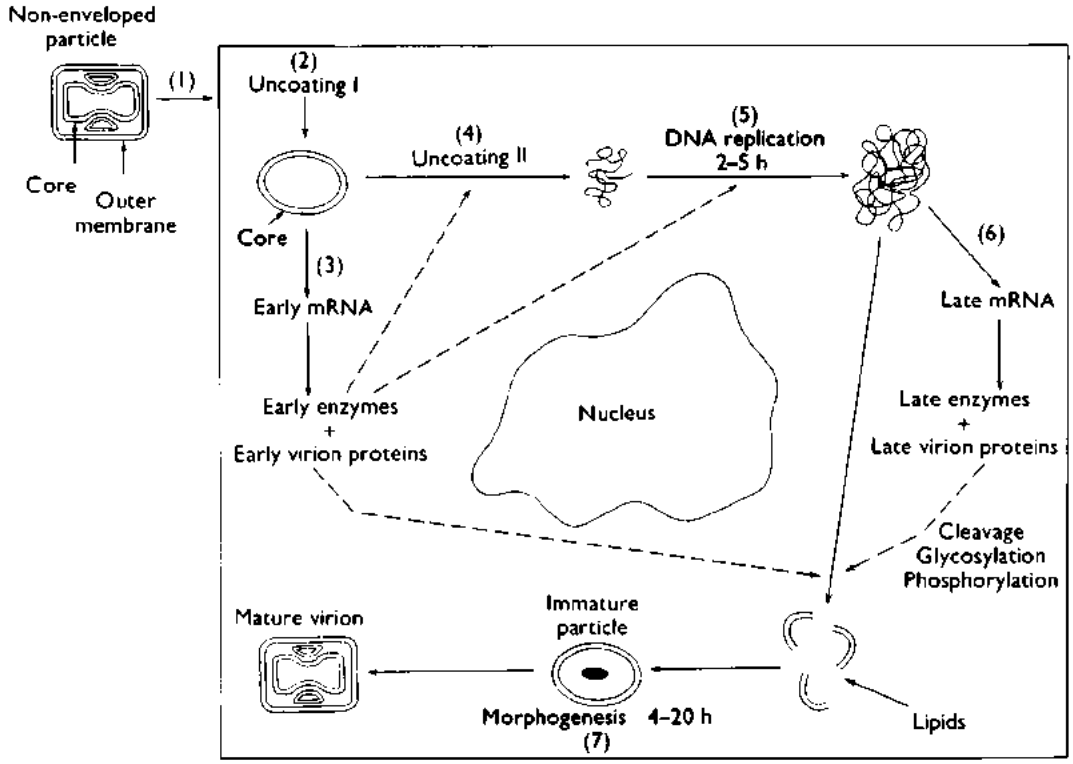


Fig. 2.3. The replication cycle of vaccinia virus. Both enveloped and non-enveloped particles are infectious but differ in their attachment to cells and mode of entry (not shown). The sequence of events is (1) attachment and entry, (2) uncoating I, whereby the outer membrane is removed by cellular enzymes, leaving the core, (3) immediate early transcription from DNA within the core by the viral transcriptase, leading to the production of early enzymes which include the enzyme that produces (4) uncoating II and release of the viral DNA into the cytoplasm. Early transcription continues and simultaneously (5) DNA replication occurs, after which (6) late transcription occurs from the newly synthesized DNA, followed by translation, and cleavage, glycosylation and phosphorylation of some of the late proteins. Morphogenesis (7) is illustrated in more detail in Fig. 2.4. (From Moss, 1985.)

development. The additional morphological changes by which the immature particle is reorganized to become a mature virion require continuing protein synthesis. Although DNA replication does not involve the activity of the cell nucleus, assembly is very inefficient in cells lacking functional nuclei.

Release

In the majority of the vaccinia-virus/cell systems that have been studied, most of the mature progeny virions remain cell-associated. Cell-associated virions are released when the cell undergoes necrosis, and they may infect contiguous cells, within a solid organ or in a cell monolayer, without ever being exposed to an extracellular environment. This occurs by the recruitment of contiguous cells into polykaryocytes (Dales & Siminovich, 1961), as well as by the necrosis of the infected cell, and is well demonstrated by the development of plaques in the presence of neutralizing antibody in the overlay medium (see Chapter 3, Plate 3.10).

Release of virions from the plasma membrane of the intact cultured cell also occurs. Tsutsui (1983) observed a simple budding process in FL cells, but more commonly mature "naked" virions acquire a double membrane envelope in the vicinity of the Golgi apparatus (Ichihashi et al., 1971; Payne & Kristensson, 1979; Plate 2.9A) and migrate to the cell surface, apparently under the influence of cytoplasmic microfilaments (Hiller et al., 1979). At the cell surface the outer of these two membranes fuses with the plasma membrane, releasing enveloped virions (Plate 2.9C and D). This process also occurs in mice infected with vaccinia virus (Payne & Kristensson, 1985).

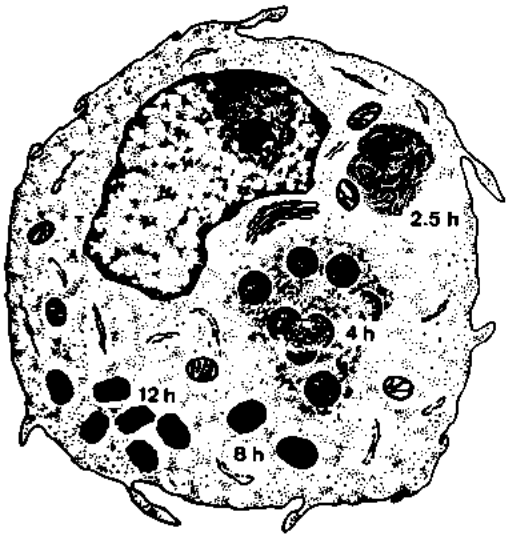


Fig. 2.4. Diagram of a cell representing the morphogenesis of vaccinia virions. The viroplasm, or viral "factory", visualized in stained cells as the B-type inclusion body, is first seen at 2.5 hours, cupules first appear at 4 hours, and some are completed as immature particles at 6–8 hours. From 8 hours onwards mature particles appear, maturation occurring within the membrane of the immature particles, which loses its spicules and acquires surface tubules. Processes involving envelopment and release are not shown. (From Moss, 1985.)

The efficiency of egress by envelopment is affected both by the type of host cell and by the strain of virus used; RK 13 cells give a high yield of enveloped virions, especially with certain strains of vaccinia virus (Payne, 1980). Routine electron microscopy of material from smallpox pustules and scabs rarely revealed enveloped virions (J. H. Nakano, personal communication, 1982). In cells infected with cowpox virus, most mature virions are usually associated with A-type inclusion bodies (see Plate 2.10).

Cellular Changes

Within one or two hours of infection, so-called "toxic" changes may occur in the infected cells, which in monolayer cultures become rounded and retract from each other (Fig. 2.5). New antigens occur on the cytoplasmic membrane very early (Ueda et al., 1972), and by the 4th hour there is cytological evidence of viral replication; basophilic areas appear in the cytoplasm—the viral "factories" of Cairns (1960). Eventually gross changes occur in the cells; depending on the particular virus–host cell combination there may be an aggregation of cells into hyperplastic foci, adjacent cells may fuse to form large polykaryocytes, or cell necrosis and rupture may occur, with release of the cell-associated virions.

Inclusion bodies

The appearances of the inclusion bodies found in orthopoxvirus-infected cells is shown in Plate 2.7. B-type inclusion bodies are irregular in shape, stain rather weakly with most histological stains and are found in all poxvirus-infected cells. They were first described in cells infected with variola and vaccinia viruses by Guarnieri (1892) and are often eponymously known as "Guarnieri bodies". It is now clear that these B-type inclusions are the cellular sites of poxvirus replication. A-type inclusion bodies, on the other hand, are usually spherical, stain brilliantly with eosin, and are characteristic of cells infected with ectromelia, cowpox and raccoonpox viruses but are not found in infection with the other orthopoxviruses. Depending on the genetic nature of the virus, A-type inclusions may contain many mature virions or be devoid of them (Plate 2.10; Ichihashi & Matsumoto, 1968). They usually appear late in infection and are not associated with viral replication.

Changes in the cell surface

Some of the earliest changes, and the most significant in relation to the immune response, are the virus-induced alterations in the plasma membranes of infected cells. Some virus-coded antigens are expressed on the surface of the cell within 2 hours of infection (Ueda et al., 1972; Amano et al., 1979); other polypeptides which develop late in infection, including the haemagglutinin and several other envelope glycoproteins, are also incorporated into the plasma membranes of infected cells (Payne, 1979). The development of membrane-associated haemagglutinin can be followed by haemadsorption tests, which have been used in the analysis of differences between variola major and alastrim viruses (Dumbell & Wells, 1982; Dumbell & Huq, 1986; see Table 2.4). Some of these viral antigens promote cell fusion and thus cell-to-cell spread of virions.

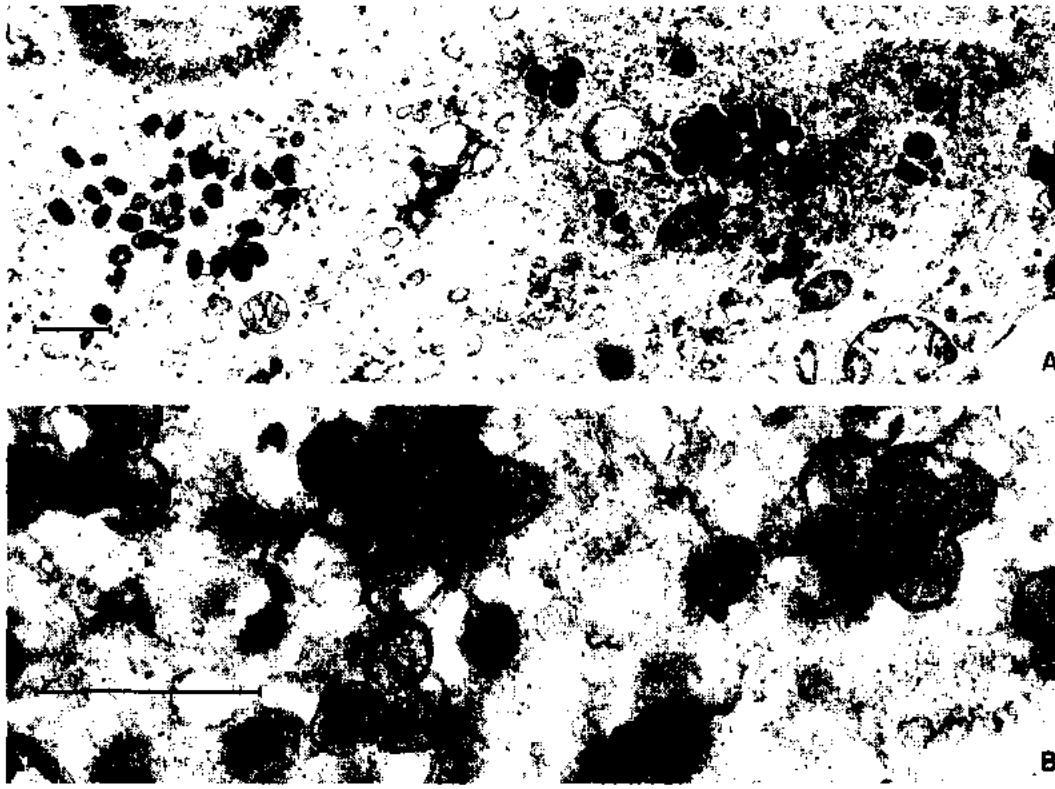


Plate 2.8. Viral morphogenesis. **A**. Infected cell showing viral "factory" area with immature particles on right; mature naked intracellular virions on left. Bar = 1000 nm. **B**. "Factory" area showing the "caps" (cupules) of developing immature viral particles. Bar = 100 nm. (**A** from Payne & Kristensson, 1979; **B** from Dales & Siminovich, 1961.)

CHARACTERIZATION OF ORTHOPOXVIRUSES BY CHEMICAL METHODS

Species, strains, and mutants of orthopoxviruses can be characterized by analyses of their DNAs, using restriction endonuclease digestion, or by an examination of gene products (polypeptides) applying serological tests or separation in polyacrylamide gels.

Comparison of Viral DNAs

Differences in DNAs of different species

The DNAs of orthopoxviruses range in size from 165 kbp for variola virus to 210 kbp for cowpox virus. The larger differences, i.e., between species, are reproducible but there is some strain variation within each species. As will be described later, deletion mutants occur quite commonly and often involve the loss of substantial fragments of DNA from one or the other end of the genome.

As illustrated in Fig. 2.2, the opposing terminal fragments of the DNAs of most orthopoxviruses contain long terminal repeats, hence they cross-hybridize. Variola virus is an exception, in that it lacks an obvious inverted terminal repeat, so that opposite termini do not cross-hybridize (Mackett & Archard, 1979; Dumbell & Archard, 1980). One end of variola DNA was found to hybridize with termini of the DNAs of other species of orthopoxviruses; the other end hybridized with a subterminal fragment of monkeypox DNA. The absence of a terminal repeat is not absolute; Esposito & Knight (1985) have shown that a very small fragment from the vaccinia DNA terminus that hybridizes well with one end of variola DNA hybridizes weakly with the other end, suggesting that there is a very small terminal repetition, less than 0.5 kbp, in variola DNA.

Major comparative studies of the DNAs of different species of orthopoxviruses have been carried out by Mackett (1981) in the United Kingdom and Esposito in the USA

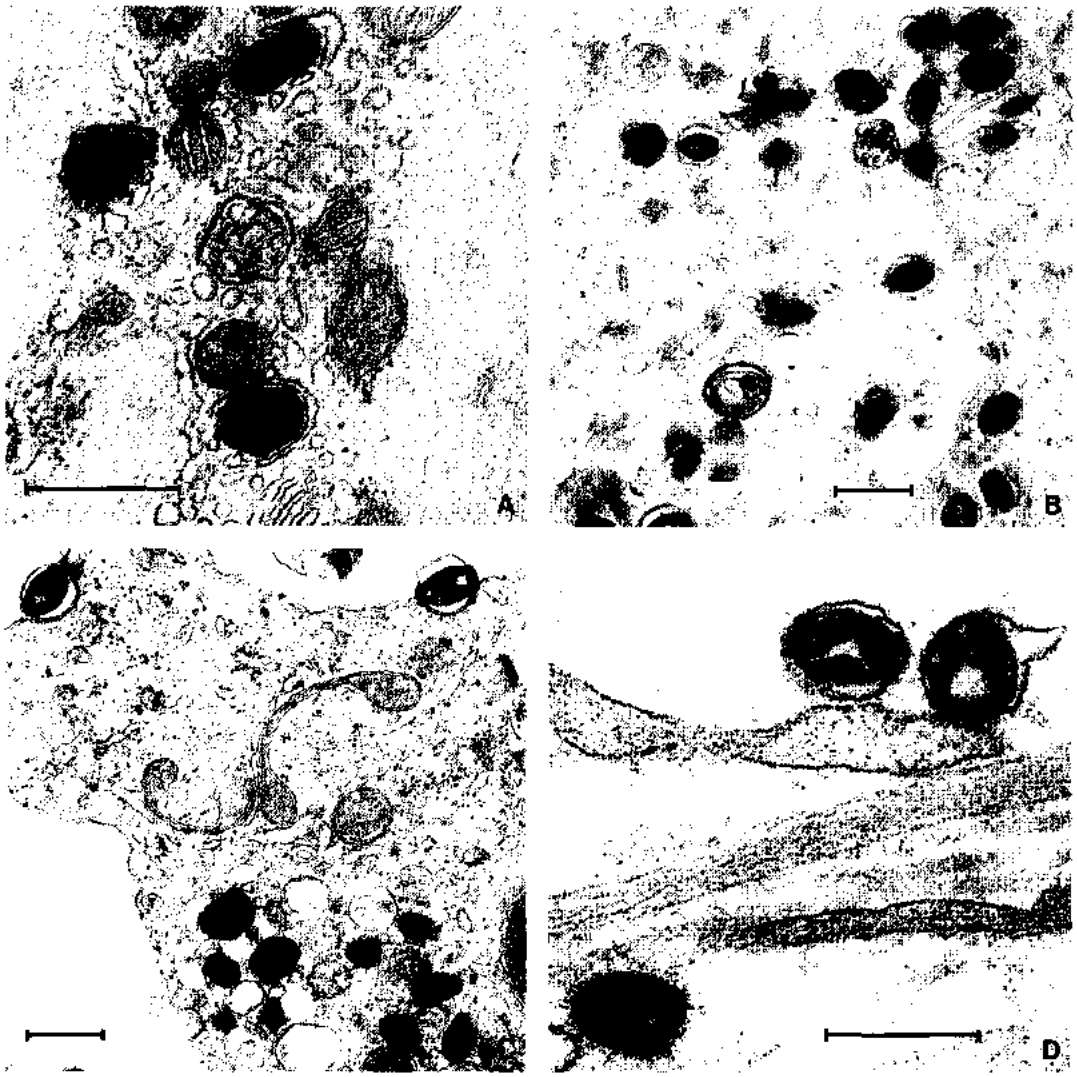


Plate 2.9. Release of enveloped virions by cells of mouse respiratory tract after infection with vaccinia virus. **A**: Acquisition of double membranes in vicinity of Golgi apparatus. **B**. Double-enveloped particles in cytoplasm of cell. **C** and **D**: Virions with a single envelope after release from cells. bars = 500 nm. (From Payne & Kristensson, 1985.)

(Esposito & Knight, 1985). In this section an attempt is made, using restriction endonuclease maps, to provide the chemical basis for the species designations that are shown in Tables 2.2 and 2.3.

Fig. 2.6 sets out the cleavage sites of the restriction endonuclease *Hin*dIII in the DNA molecules of strains of each of the 8 species of *Orthopoxvirus* for which such maps are available. Uasin Gishu disease virus DNA has not yet been analysed by restriction endonuclease digestion. Several *Hin*dIII fragments of raccoonpox virus DNA (the only species of *Orthopoxvirus* yet found to be endemic in the Americas) cross-hybridize with those of other *Orthopoxvirus* species, but not at all with *Hin*dIII fragments of DNAs of mammalian poxviruses of other genera (*Leporipoxvirus, Parapoxvirus*) found in North America. However, the "map" of raccoonpox virus does not lend itself to comparisons by the computer program used for producing Fig. 2.7. The large central conserved area of all the DNAs that have been mapped is readily apparent in the *Hin*dIII maps. The close resemblance between the representative strains of particular species (shown in greater detail in Fig. 2.9 and 2.10, and Chapter 29, Fig. 29.1 and 29.4)

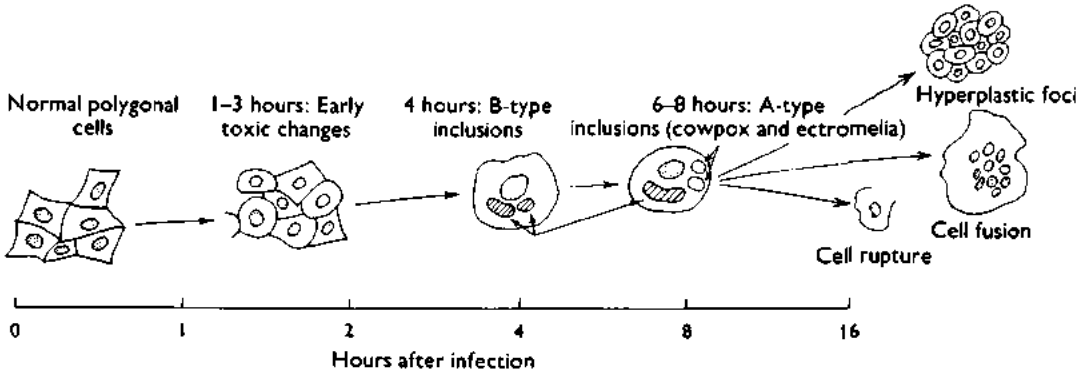


Fig. 2.5. Cellular changes seen at various times (logarithmic scale) after infection of a monolayer of cultured cells.

and the differences between species, particularly towards the ends of the molecule, are apparent, but it is difficult to appreciate these quantitatively by visual inspection of restriction maps. The similarities and differences are brought out better by the dendrogram (Fig. 2.7). On the basis of this kind of analysis it is possible to distinguish clearly between all species of *Orthopoxvirus* that have been mapped. Other analyses, involving several strains of each of several species in a single dendrogram (Fenner et al., WHO/SE/80.154), showed that all strains of each species clustered together and species remained clearly separable.

Changes in DNA associated with mutation and recombination

The foregoing description of the structure and composition of orthopoxvirus DNA may have given the impression that the DNAs of various species are fixed. To some extent this is true; however, minor changes due to mutation occur very frequently and deletion mutations, which are known to occur commonly among the orthopoxviruses with a wide host range (vaccinia, cowpox and monkeypox viruses), can be associated with losses of substantial amounts of viral DNA. Furthermore, different strains and species of *Orthopoxvirus* recombine readily when single cells are subjected to mixed infection, with associated changes in the DNA.

Diversity in DNA molecules may be readily generated within a species, presumably by "autorecombination" during replication. For example, the terminal fragments of vaccinia DNA may become heterogeneous in length (Wittek et al., 1978), as does the internal junction fragment of white pock mutants of cowpox virus (Archard et al., 1984). These heterogeneities can be eliminated, at least temporarily, by cloning the virus. Indeed, cloning, by the growth of stocks from single pocks or plaques, is an obligatory procedure if stocks of relative genetic homogeneity are required. For example, both Fenner (1958) and Ghendon & Chernos (1964) found that stock preparations of several different strains of smallpox vaccine contained virus that produced mixed pocks (ulcerated and non-ulcerated), which could be separated by cloning.

The most important kind of mutation, from the point of view of the global smallpox eradication campaign, were the white pock mutants of monkeypox virus (see Chapter 30). All orthopoxviruses that produce ulcerated (haemorrhagic) pocks on the CA membrane (cowpox, monkeypox and neurovaccinia strains of vaccinia virus, including rabbitpox virus) produce non-ulcerated (white) pocks with a frequency (from cloned preparations) that varies between 0.1% and 0.01%. In all cases in which several white pocks have been examined, most mutants obtained from a single cloned preparation have been different (Gemmell & Fenner, 1960; Dumbell & Archard, 1980), and the majority of such mutants involve large deletions from one or the other end of the genome, which are often associated with transpositions (Archard et al., 1984; Moyer & Rothe, 1980; Dumbell & Archard, 1980). In spite of these major changes in the amount of DNA, the rest of the genome map is recognizably that of the parental virus (see Chapter 30, Fig. 30.2).

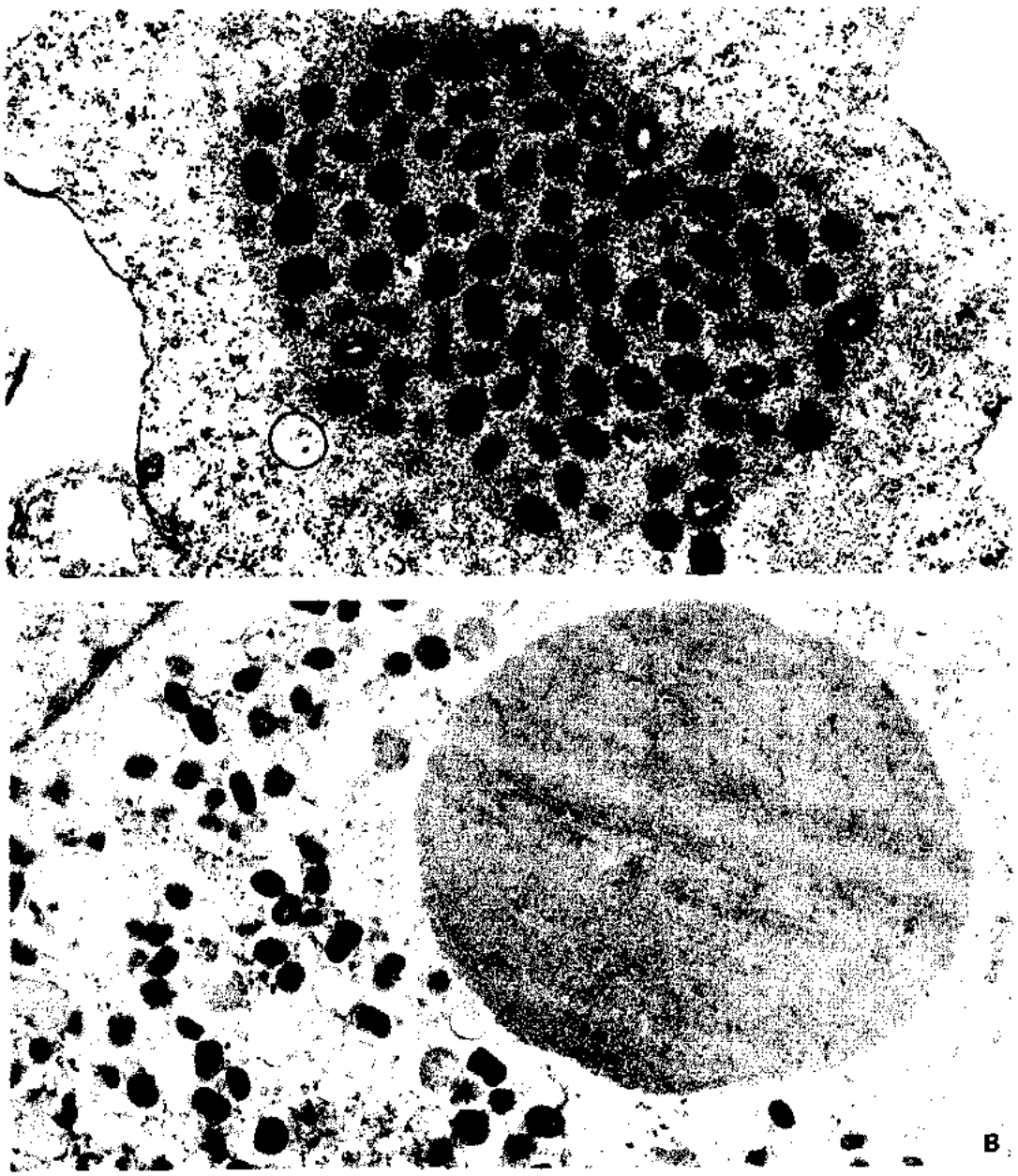


Plate 2.10. A-type inclusion bodies produced by cowpox virus. Depending on the genetic characteristics of the strain, the inclusion body may contain large numbers of virions (**A**), or none at all (**B**).

Comparison of Viral Polypeptides

Serological tests

The earliest methods of comparing the polypeptides of different orthopoxviruses were based on serological tests. All orthopoxviruses show substantial cross-reactivity in tests for neutralization of infectivity, although differences between species and strains can be demonstrated by absorption tests (Baxby, 1982a). Gel-diffusion tests, which had been shown to distinguish over 20 different antigens in cells infected with rabbitpox virus (Appleyard & Westwood, 1964a), provided an obvious method for attempting the serological differentiation of different species of *Orthopoxvirus*. Using absorbed sera, Gispen & Brand-Saathof (1974) and subsequently Esposito et al. (1977a)

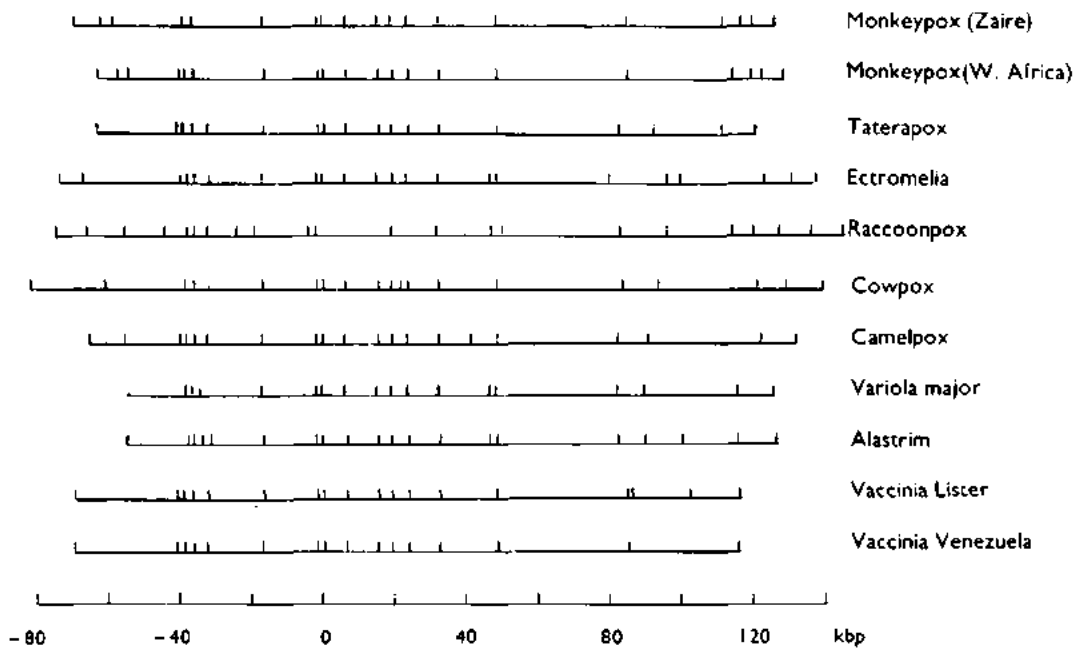


Fig. 2.6. Physical map locations of *Hin*dIII restriction sites in the DNAs of 8 of the recognized species of *Orthopoxvirus*. Origin of DNAs: Monkeypox (Zaire)—Congo 1970, an isolate from a human case in Zaire; Monkeypox (W. Africa)—Copenhagen, an isolate from monkey, probably originating in West Africa; Taterapox —Benin isolate; Ectromelia—Hampstead strain; Raccoonpox—isolate from Maryland; Cowpox—Brighton strain; Camelpox—Somalia 1248; Variola major—Harvey strain; Alastrim—Butler strain; Vaccinia—Lister and Venezuela strains. (Data from Esposito & Knight, 1985.)

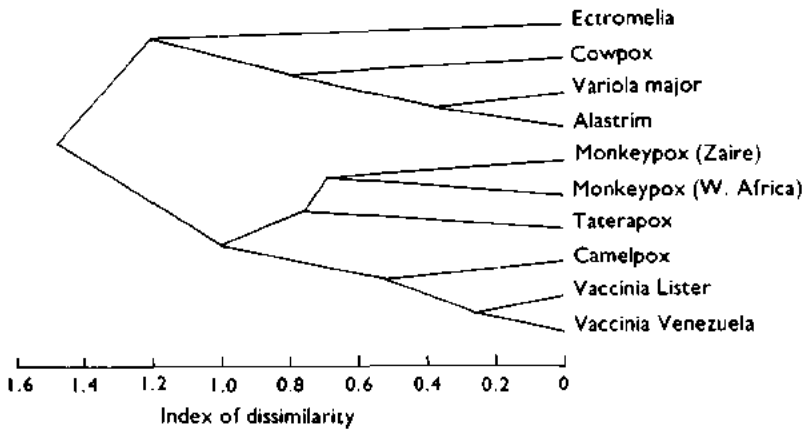


Fig. 2.7. Dendrogram illustrating the similarities and differences between the DNAs for which restriction sites are shown in Fig. 2.6 (except for raccoonpox DNA). Presence, absence or impossibility of sites (because the DNA molecules were too small) were analysed as described by Gibbs & Fenner (1984) using the squared Euclidean metric (number of attributes = 45). The "index of dissimilarity" has no absolute value, but the dendrogram shows that pairs of viruses of the same species (variola, monkeypox and vaccinia) resemble each other more than any other species. Such comparisons are developed with larger numbers of strains of various orthopoxviruses in Fig. 2.9 (variola virus), Fig. 2.10 (vaccinia virus), and in Chapter 29, Fig. 29.1 (monkeypox virus) and Fig. 29.4 (cowpox virus).

demonstrated species-specific antigenic patterns for variola, vaccinia and monkeypox viruses. Maltseva & Marennikova (1976) used absorption in the test well of gel-diffusion plates to distinguish between variola, monkeypox, vaccinia and cowpox viruses and showed that isolates from a number of different animals in outbreaks in zoos (okapis, elephants, and various carnivores) reacted like cowpox virus.

Immunofluorescence (Gispen et al., 1974), radioimmunoassay (Hutchinson et al., 1977) and ELISA (Marennikova et al., 1981) have also been used for differentiating variola-, monkeypox- and vaccinia-specific antisera, after absorption of the tested sera with homologous and heterologous antigens. All methods were effective in allowing specific diagnoses of monkeypox infection to be made with certain monkey sera. However, while absorption tests are usually successful in demonstrating specific antibodies in high-titre sera, they fail with sera of low titre, such as are often found in sero-epidemiological surveys. Further, sensitive tests such as radio-immunoassay-absorption require antisera to the gamma-globulins of the species under test; such antisera are available for monkeys but not for most other species of wild animal. Thus these tests are unsuitable for routine use with sera from a range of different animals, such as are usually collected during ecological surveys.

Comparisons of polypeptides in one-dimensional polyacrylamide gels

Virion polypeptides (Esposito et al., 1977b; Arita & Tagaya, 1980), core polypeptides (Turner & Baxby, 1979) and late intracellular polypeptides (Harper et al., 1979) from several species and isolates of orthopoxviruses have been analysed in one-dimensional polyacrylamide gels. Several differences between species were noted, as were similarities between viruses of uncertain affinities ("Lenny", MK-10-73, buffalopox; see later) and vaccinia virus. However, bands in such gels are identified only by their size and may include monomers and multiplers. This disadvantage is lessened when additional information is provided by two-dimensional gels or immunoprecipitation (Ikuta et al., 1979). DNA analysis is at present a simpler and more reliable basis for the identification of orthopoxviruses, but immunoprecipitation may be important in the process of developing species-specific monoclonal antibodies.

SUMMARY: DISTINCTIONS BETWEEN ORTHOPOXVIRUSES

Poxviruses have larger and more complex virions than most other animal viruses. As a consequence, neutralization tests, which with most viral families are the best method of distinguishing between viral species, are useful only at the generic level, and cross-neutralization (or cross-protection) provides the most reliable method of allocating an unknown poxvirus to the genus *Orthopoxvirus*.

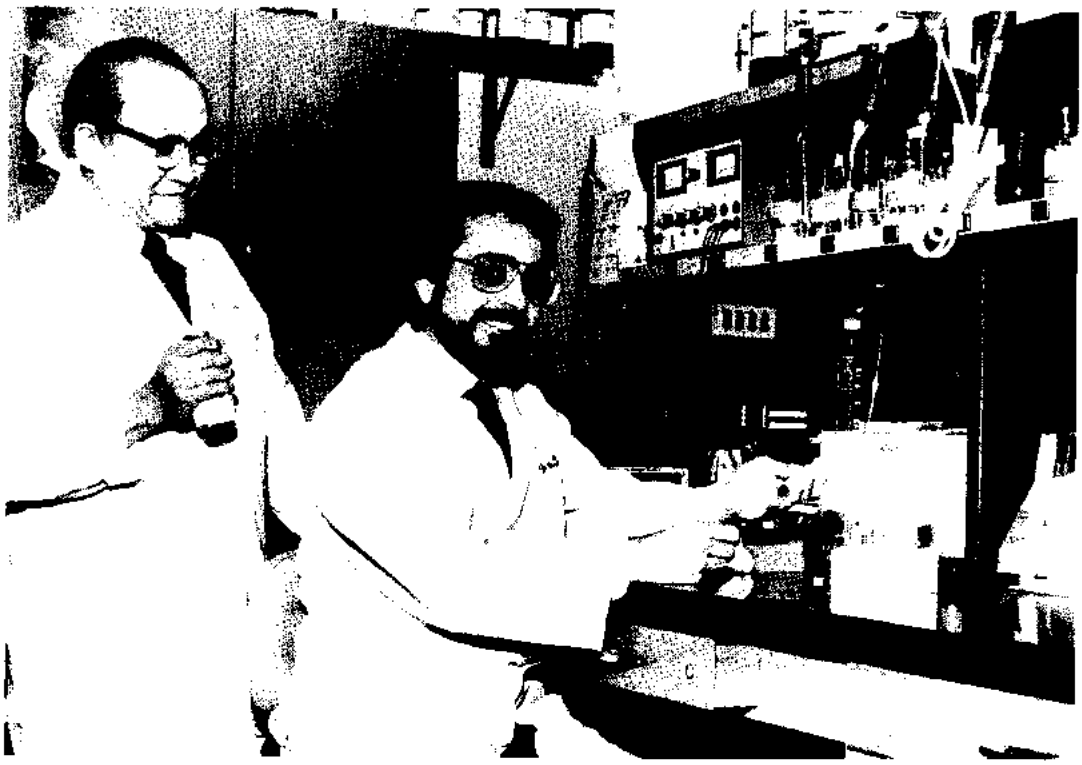
However, although there is extensive cross-neutralization between all members of the genus, several distinct species exist which differ from one another in a number of biological characteristics, in the size and structure of the genome and in polypeptide composition. Several species are represented by very few independent isolates (ectromelia, camelpox, taterapox, raccoonpox and Uasin Gishu disease viruses), but the properties of the few (or single) isolates of each of these justifies its differentiation as a distinct species. The other 4 species are each represented by many strains, recovered at different times and places.

Variola virus has only been recovered from human subjects and although strains occur which have very different levels of virulence for man, all share many other biological properties and all have very similar genomes.

The other 3 species have wide host ranges. Vaccinia virus has been recovered from a variety of domestic animals and some strains can maintain themselves in nature in rabbits, cows and buffaloes, at least for limited periods of time. However, it seems likely that such infections have originated from human sources. All strains of vaccinia virus share many biological properties and have very similar genomes. Cowpox virus has been recovered from a variety of naturally infected animals, in Europe and the western USSR, but is probably a natural disease of rodents (see Chapter 29). All strains share as characteristic biological properties the production of bright-red haemorrhagic pocks on the CA membrane and the production of A-type as well as B-type cytoplasmic inclusion bodies. Most have larger genomes than those of other orthopoxviruses. Monkeypox virus appears to occur in nature only in western and central Africa, and has been recognized only when infections have occurred in laboratory primates and in man, and once in a wild squirrel. The biological properties of different isolates are very similar, but strains originating from western Africa have rather different genome maps from those recovered in Zaire (see Chapter 29, Fig. 29.1).

VARIOLA VIRUS

The biological properties of variola virus are enumerated in Table 2.3 and its DNA is



CENTERS FOR DISEASE CONTROL, 1984

Plate 2.11. *Left:* James Hiroto Nakano (b. 1922). The leading American expert on the diagnosis of poxvirus infections. Head of the WHO Collaborating Centre in the Centers for Disease Control, Atlanta, GA, USA, since 1971. Active in much WHO-sponsored research on orthopoxvirus infections and a member of several WHO expert groups on poxvirus infections. *Right:* Joseph John Esposito (b. 1942). A molecular biologist working at the Centers for Disease Control, Atlanta, GA, USA, who has been responsible for much of the mapping of the DNAs of variola, monkeypox and "whitepox" viruses described in the present chapter and in Chapters 29 and 30.

compared with that of other species of *Orthopoxvirus* in Fig. 2.6. It is a specifically human virus, with a narrow host range in laboratory animals, and can be readily distinguished from other orthopoxviruses that can infect man by the distinctive small white pocks produced on the CA membrane (see Plate 2.5).

Isolation from Natural Sources

Apart from a few bizarre occurrences, such as the infection of a performing monkey described by Mack & Noble (1970), variola virus has been found in nature only as a specifically human pathogen, and thousands of isolations have been made from infected humans. Reported recoveries of variola virus from animal sources (the so-called "whitepox" viruses), described in Chapter 30, are not regarded as providing an exception to this statement.

Variola Major and Variola Minor

Observations on outbreaks of smallpox in the USA and South Africa at the end of the 19th century and in the USA and the United Kingdom during the early 20th century led to the recognition that, regardless of the vaccination status of the community involved, some epidemics were associated with a high mortality and others with a low mortality (see Chapter 1). Painstaking epidemiological studies by Chapin & Smith (1932) showed that the novel mild variety of smallpox recognized in the USA early in the 20th century "bred true" and never reverted to the severe variety, either in the USA or when it was transported to other parts of the world. This variety of smallpox was called variola minor and the classical form variola major.

Subsequent studies in different geographical areas showed that strains of variola virus which occurred in various parts of the world differed in their virulence for man, producing

case-fatality rates in unvaccinated individuals that ranged from less than 1% to about 40% (see Chapter 4). However, for practical purposes only two clinico-epidemiological varieties of smallpox were recognized: variola major (case-fatality rates, 5–40%) and variola minor (case-fatality rates, 0.1–2%). Recent laboratory studies of strains of variola minor virus recovered from Africa and the USA (or from countries with variola minor originally derived from the USA) revealed that these two groups of variola minor viruses differ in several characteristics (Dumbell & Huq, 1986); it is convenient to distinguish them by calling the USA-derived strains alastrim virus and the other strains African variola minor virus.

Plate 2.12. Keith Rodney Dumbell (b. 1922). A leading British virologist who has been involved in studies of variola virus and other orthopoxviruses since 1946. He was head of the WHO Collaborating Centre for Poxvirus Research at St Mary's Hospital Medical School, London, England, from 1969 to 1981, and was a member of the Global Commission and several WHO expert groups on poxvirus infections.

Laboratory Investigations with Variola Virus

Because of its danger, variola virus was studied much less than vaccinia virus in the laboratory, especially in recent years, after smallpox had been eliminated from most of the countries in which sophisticated laboratory investigations could be carried out. Laboratory investigations were focused on three aspects: (1) the devising of a diagnostic procedure for the recognition of variola virus; (2) finding correlates in laboratory animals of virulence for man; and (3) during recent years, a comparison of the DNAs of strains of variola virus obtained from different parts of the world and the comparison of the DNAs of variola virus and other orthopoxviruses.

Pathogenicity for Laboratory Animals

Variola virus was one of the first viruses to be inoculated in laboratory animals, when tests were carried out in monkeys and in cows (in attempts to develop strains of "vaccine"). Subsequent investigations showed that it had a much narrower host range than the other orthopoxviruses that infect man (cowpox, monkeypox and vaccinia viruses), and usually produced smaller or less severe lesions than these viruses in the laboratory animals that were suceptible.

All strains of variola virus produce small white pocks on the CA membrane of developing chick embryos (Plate 2.5); this is the most useful laboratory test for differentiating variola virus from other poxviruses in material derived from human subjects. The pocks reach a diameter of 0.3–0.6 mm after 3 days' incubation. They are uniform in size, raised above the surface and have clearly demarcated margins. Unlike camelpox virus, the pocks of which develop a small haemorrhagic centre when the eggs are incubated at 35 °C, the pocks produced by variola virus retain their characteristic opaque white appearance at all temperatures. Experienced laboratory workers can accurately differentiate variola virus from all other poxviruses by this test alone.

Another simple and useful test for differentiating variola virus from monkeypox, vaccinia and cowpox viruses is intradermal inoculation in rabbits, since of these four agents only variola virus fails to produce a large and obvious lesion (Plate 2.6). Dumbell & Bedson (1966) showed that variola virus could be adapted to grow serially in rabbit skin if first passed several times in rabbit kidney cell cultures. It then produced a small nodular lesion at the site of intradermal inoculation, but newly isolated and unadapted strains did not produce transmissible lesions in rabbits, although large doses pro-

duced erythema and a small transient papule at the inoculation site.

Some non-human primates are highly susceptible to infection with variola virus and suffer from a disease with a generalized rash, which may be severe and sometimes lethal in chimpanzees and orang-utans. The symptomatology and pathogenesis of primate smallpox are discussed in Chapter 3.

Tests in cows

During the 19th century the cow was often inoculated with variola virus, in efforts to obtain new strains of "variolae vaccinae" for human vaccination. The old literature contains many claims of success for this procedure, largely from German authors—and claims to the contrary, largely from French authors. Some older accounts, although lacking the precision possible with modern virological methods, provide interesting clues about the claimed "transformation" of variola virus into vaccinia virus by passage in cows. Fleming (1880), in a wide-ranging review, considered that after intradermal inoculation variola virus sometimes produced a small lesion in the skin of the cow, from which passage of material to humans caused inoculation smallpox. He supported French authorities such as Chaveau in saying that variola virus could not be carried in series in cows, although in individual cases early passage inoculations might render them resistant to challenge with cowpox or vaccinia virus.

The most recent experiments in cows are those reported by Herrlich et al. (1963), who inoculated 10 calves with very large doses of variola major virus. Only one reacted with small papules, from which variola virus was recovered but the virus could not be further passaged in cows. Only the animal that reacted was found to be immune when subsequently challenged with vaccinia virus.

Growth in Cultured Cells

In contrast to its limited host range in laboratory animals, variola virus will grow and produce a cytopathic effect in cultured cells derived from many species (Hahon, 1958; Pirsch et al., 1963). However, it grows best in cells from humans and other primates in which it produces characteristic "hyperplastic" foci. In fact, this appearance (Plate 2.13) is not due to proliferation of the infected cells, but to their aggregation. Because of the low cytopathogenicity of variola virus, infected cells remain in the monolayer and are pushed together by the growing non-infected cells around them (Ono & Kato, 1968). Kitamura (1968) described an assay of variola virus based on counting the hyperplastic foci that develop in HeLa and FL cells (Plate 2.13); in primate cells (Vero and JINET) these foci progress to form small plaques (Tsuchiya & Tagaya, 1970).

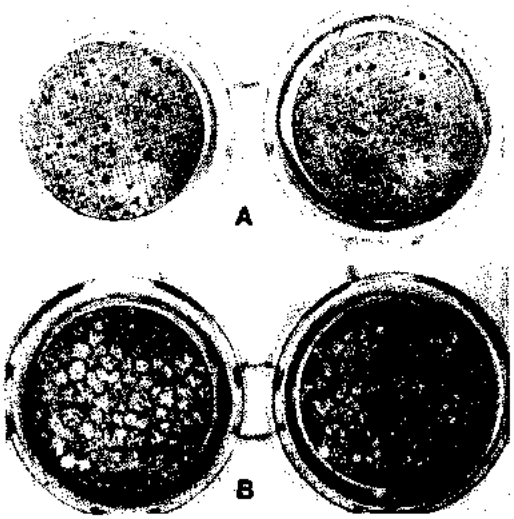


Plate 2.13. Hyperplastic foci produced in HeLa cell monolayers by variola virus (**A**) and lytic plaques produced by vaccinia virus (**B**). (Similar large plaques are also produced by monkeypox and cowpox viruses.) Monolayers are in the bottom of Microtiter plates, the wells being 6 mm in diameter. Incubation for 48 hours before staining. (From Kitamura & Tanaka, 1973.)

Variola virus will replicate and produce a cytopathic effect in continuous-line pig embryo kidney cells (Marennikova et al., 1971), a test which has been used to differentiate it from monkeypox virus. However, Veda & Dumbell (unpublished observations, 1974) found that different strains of monkeypox virus varied in their capacity to grow and produce a cytopathic effect in pig embryo kidney cells; some hardly grew at all, others grew moderately well, but none grew as well as variola or vaccinia viruses.

Haemadsorption

Some of the haemagglutinin that is produced during orthopoxvirus infections appears in the cytoplasmic membrane of the

Table 2.4. Haemadsorption in human embryo fibroblasts incubated at 40 °C for 48 hours after being infected with variola virus at a multiplicity of infection of 1 plaque-forming unit per cell[a]

Variety of smallpox	Sources of isolates	Type of haemadsorption		
		Confluent	Focal	Absent
Asian variola major	United Kingdom	15	4	0
	Pakistan	18	8	0
African variola major	Kenya	25	18	0
	United Republic of Tanzania	2	20	0
	Western Africa	2	39	0
Alastrim	Europe and Brazil	0	5	27
African variola minor	Botswana and Ethiopia	6	15	1

[a] From Dumbell & Huq (1986).

infected cells. When susceptible erythrocytes are added to an infected culture they attach to infected cells, a phenomenon known as haemadsorption. Dumbell & Huq (1986) investigated haemadsorption in human embryo fibroblast cultures which were incubated at 40 °C for 48 hours after inoculation with different strains of variola virus. Haemadsorption was classified as confluent, focal or absent (Table 2.4).

Isolates giving confluent haemadsorption were in the majority among the Asian variola major strains and accounted for over half of the Kenyan isolates. Focal haemadsorption was characteristic of most of the other African isolates, but only a few isolates of either Asian variola major or alastrim viruses reacted in this way. Failure to elicit haemadsorption under the conditions of this test was characteristic of the alastrim virus isolates, and, apart from these, was found only in a single isolate from Ethiopia, which was also like alastrim virus in its failure to produce pocks at 38.3 °C (see Fig. 2.8).

Dumbell & Wells (1982) showed that at 38 °C alastrim virus was inhibited in activities that included the insertion of haemagglutinin into the cell membrane (and hence haemadsorption) and release of virus from the cells, although intracellular maturation proceeded normally; strains of variola major virus and most African strains of variola minor virus showed no such inhibition at 38 °C.

Thymidine kinase activity

Thymidine kinase is an enzyme which occurs in all cells, since it is essential for DNA metabolism. However, all orthopoxviruses produce a virus-coded thymidine kinase in infected cells (Moss, 1978; Bedson, 1982).

Esposito & Knight (1984) have sequenced the thymidine kinase genes of vaccinia, variola and monkeypox viruses; each differs from the other by some dozen nucleotides (out of 534) and some 5 amino acids (out of 178). Bedson (1982) showed that thymidine kinase produced by each of 11 strains of variola virus (irrespective of geographical origin) was more sensitive to feedback inhibition by thymidine triphosphate than that of any other species of *Orthopoxvirus* (see Table 2.3).

K. McCARTHY, 1971

Plate 2.14. Henry Samuel Bedson (1929–1978). A leading British virologist, who worked on various aspects of variola and "whitepox" viruses. He was Professor of Microbiology at the University of Birmingham and a member of the WHO Consultative Group for Poxvirus Research.

Laboratory Tests for Virulence

It would clearly have been useful to devise laboratory tests which might have indicated the virulence for man of different strains of

variola virus. Most studies addressed themselves to the problem of differentiating strains that caused variola minor from those that caused variola major. Several tests, outlined below, satisfactorily differentiated strains of alastrim virus derived from the Americas from strains that caused variola major. However, none of these tests distinguished strains of variola minor virus originating in Africa from variola major virus (Dumbell & Huq, 1986).

Pathogenicity for chick embryos

The first demonstration of a difference between strains of variola major and alastrim viruses in laboratory animals was the finding by Dinger (1956) that variola major virus grew better than alastrim virus in chick embryos. Helbert (1957) then showed that the amounts of variola major and alastrim viruses recovered from the CA membrane in embryos incubated at 35–36 °C were almost the same, but that there was a much higher concentration of virus in the livers of embryos inoculated with variola major virus, and a higher mortality. Dumbell et al. (1961) showed that the mortality was temperature-dependent; both varieties killed embryos at 35 °C but only variola major did so at 37 °C.

Dumbell & Huq (1986) further elaborated Helbert's test of pathogenicity for chick embryos and showed that different strains of variola virus showed a wide spectrum of response which was not strictly correlated with either virulence or geographical origin. Most strains of Asian variola major virus were of high or moderate pathogenicity. The 8 strains of alastrim virus that were tested were of low or moderate pathogenicity, but strains of variola minor virus from Botswana and Ethiopia showed much the same spectrum of pathogenicity (moderately high to low) as did strains of variola major virus from Kenya. Sarkar & Mitra (1967) reported that different strains of Asian variola major virus differed in their pathogenicity for the chick embryo in eggs incubated at 36 °C.

Ceiling temperature

Nizamuddin & Dumbell (1961) developed a simple test which reflected the greater temperature sensitivity of growth of alastrim virus compared with variola major virus. A comparison of the numbers of pocks produced on the CA membrane at 35 °C and 38.3 °C allowed an unequivocal distinction to be made between the viruses of variola major and alastrim: variola major virus produced pocks at 38.3 °C but alastrim virus did not. The difference in the temperature sensitivity of viral growth (ceiling temperature) of these two varieties of variola virus could be determined equally well in some lines of cultured cells (Kitamura & Tanaka, 1973).

Subsequent studies confirmed the value of the ceiling temperature as a criterion for

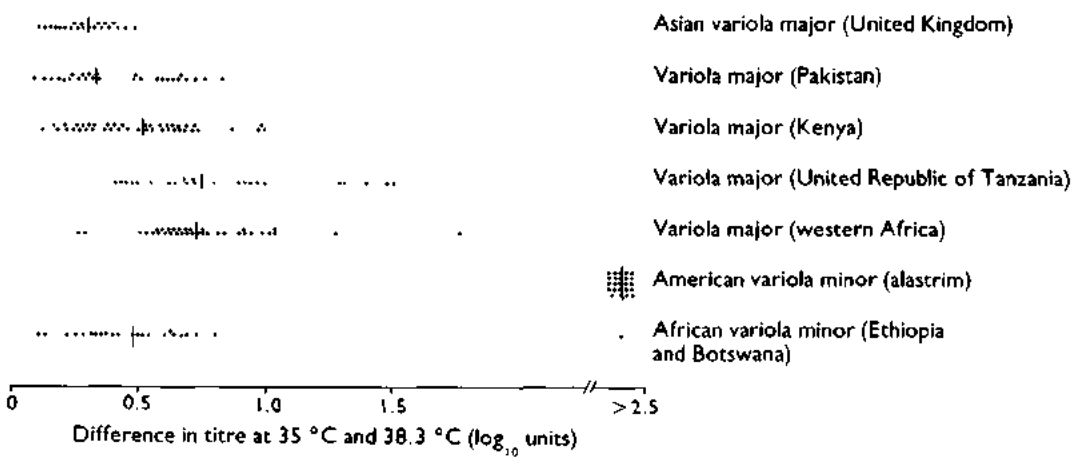


Fig. 2.8. Differences in log titre when incubating each of 196 variola virus isolates from different geographical regions on the chorioallantoic membrane at 35 °C and 38.3 °C. The larger the difference in titre, the greater the sensitivity to a raised temperature (i.e., the lower the ceiling temperature). Each dot is the result of assays of a single isolate; the vertical line shows the median observation for each group of isolates. Alastrim virus = strains of variola minor virus from South America and Europe, originally derived from the Americas. (From Dumbell & Huq, 1986.)

distinguishing alastrim virus (Downie et al., 1963), but strains of variola minor virus of equal or lower virulence from Africa (Botswana, Ethiopia) could not be differentiated from variola major virus by this test (Dumbell & Huq, 1986; Fig. 2.8). One isolate of variola minor virus from Ethiopia stood apart from all others tested in that it resembled alastrim virus in having a low ceiling temperature and failing to produce haemadsorption (Table 2.4). In an earlier study of 61 isolates of variola virus from different geographical locations, including 6 strains from Ethiopia, Shelukhina et al. (1979a) found one Ethiopian strain which resembled alastrim virus in its ceiling temperature and its virulence for mice and chick embryos. The other 5 strains from Ethiopia could not be distinguished from variola major virus by laboratory tests, although they were collected at a time when only variola minor was occurring in Ethiopia.

Initial studies (Bedson et al., 1963; Dumbell & Huq, 1975) suggested that some East African strains that showed lower virulence than Asian variola major were intermediate between variola major and alastrim viruses in their ceiling temperatures. However, attempts to define an "intermediate" strain of variola virus were not successful (Fig. 2.8). Kitamura et al. (1977b), using the temperature sensitivity of the capacity to produce foci in HeLa cells, found that 4 out of 55 strains of variola major virus recovered in India in 1975 were of the "intermediate" level of temperature sensitivity described for some East African strains.

Differences in the Virulence of Strains of Variola Major Virus

Another problem, which was studied especially by Sarkar & Mitra (1967, 1968), was whether very severe cases of variola major (haemorrhagic-type and flat-type smallpox, which were almost invariably fatal—see Chapter 1) were caused by more virulent strains of variola major virus than those that caused discrete ordinary-type smallpox. They claimed that strains of variola virus recovered from cases of haemorrhagic-type smallpox were highly virulent for both chick embryos and suckling mice much more frequently than strains derived from discrete ordinary-type smallpox, and suggested that the virulence of the virus was one component in determining the severity of cases of variola major. However, epidemiological evidence indicates that it was not the most important factor in determining whether a person would suffer from the rare haemorrhagic-type smallpox; physiological factors in the host were probably more important.

On general biological grounds, and by analogy with myxomatosis, a disease in which the assessment of virulence for the natural host was possible by direct testing (see box), it would be expected that a number of strains of variola virus which differed slightly or perhaps substantially in their virulence for man might be circulating at any time in countries in which smallpox was endemic. Because of complexities such as the degree of accuracy of information on cases and/or deaths, the interval since vaccination (if applicable) and age-related differences in case-fatality rates, it was rarely possible to utilize data from smallpox outbreaks other than to determine whether the cause was very mild smallpox (variola minor) or variola major. The significance of apparent differences in case-fatality rates in different outbreaks of variola major were virtually impossible to assess, although most outbreaks in Africa in the 1960s and 1970s had lower case-fatality rates (see Chapters 17–20) than those of variola major in mainland Asia. Unfortunately, except for ceiling temperature tests with alastrim virus, there was no laboratory test of which the results were invariably correlated with virulence for man.

Comparison of the DNAs of Strains of Variola Virus

Restriction endonuclease digests of 6 strains of variola virus, derived from outbreaks of variola major and variola minor in Africa, Asia, and Europe, were analysed at the Centers for Disease Control, Atlanta, USA (Esposito et al., 1978; Esposito & Knight, 1985). Physical map locations of the sites of cleavage by the enzyme *Hin*dIII are compared in Fig. 2.9. Minor differences existed between most strains, but there were no special relationships that correlated with either the virulence of these strains for man or their geographical distribution. All the variola DNAs were clearly very different from those of vaccinia and monkeypox viruses. By comparing gels of DNA fragments from several isolates of variola virus, K. R. Dumbell (personal communication, 1984) showed that DNAs from 4 alastrim strains were

Variation in the Virulence of Poxviruses

It is notoriously difficult to develop laboratory tests to determine the virulence of viruses. The best that can be done is to test the lethality of virus strains in laboratory animals of the same species as those in which the disease is spreading naturally. For variola virus, virulence tests in man were clearly impossible, and they were not practicable in primates. Sarkar tested many strains of variola major virus from Calcutta in chick embryos and baby mice and produced some evidence of differences in virulence for these hosts that appeared to be correlated with virulence for man, but other virologists were unable to reproduce these results, although few attempted to do so. Further, the fact that the highly lethal haemorrhagic-type smallpox usually produced discrete ordinary-type smallpox in case contacts led most epidemiologists to question the relevance of these results. Certain laboratory tests were successfully used for distinguishing one strain of variola virus of low virulence (alastrim virus) from variola major virus, but failed to distinguish between the equally mild African variola minor virus and variola major virus (Dumbell & Huq, 1986).

The variations in virulence that might be expected in a poxvirus that has been spreading naturally for some years can be assessed in animal models. Myxomatosis in the rabbit, *Oryctolagus cuniculus*, provides a good example, in which the lethality and survival times in groups of rabbits were used as the test for virulence of the virus (Fenner & Ratcliffe, 1965; Fenner, 1983). Two different strains of myxoma virus (a member of the genus *Leporipoxvirus*) were used to initiate the disease among wild rabbits in Australia and Europe, and it became enzootic in both continents. Initially both introductions caused very high mortalities (over 99% case-fatality rates), but within a few years tests of the virus in genetically unselected laboratory rabbits showed that a wide range of strains of different virulence had evolved, although no strain has yet been recovered from naturally infected rabbits that is as attenuated as some strains derived by laboratory manipulation. This example shows that with a virus that was initially extremely virulent, several different strains which differed substantially in virulence arose within a few years and persisted in nature. This development occurred within a decade; it seems highly likely that a similar range of strains of variola virus of different virulence for man occurred in countries in which smallpox had been endemic for centuries.

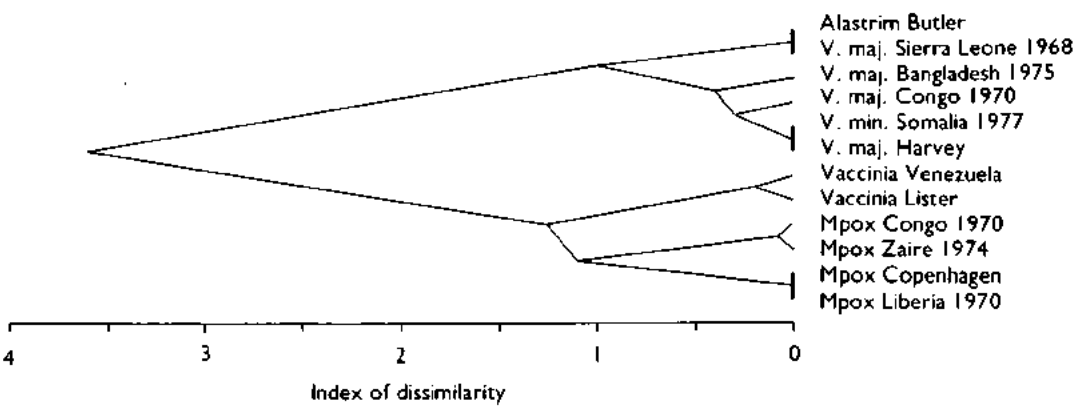


Fig. 2.9. Dendrogram illustrating the similarities and differences between *Hin*dIII cleavage sites on 6 variola DNAs, compared with 4 monkeypox and 2 vaccinia DNAs (see legend of Fig. 2.7). Number of attributes = 36. Origin of DNAs as indicated; V. maj. = variola major; V. min. = variola minor; Mpox = monkeypox. Full details of the origins of the viral strains are given in Esposito & Knight (1985), from which the data on restriction sites were derived.

similar but differed from the DNA of the classical variola major strain, Harvey, whereas the DNAs of all the variola minor isolates from Africa (Botswana, Ethiopia and Somalia) resembled that of Harvey, rather than those of alastrim virus.

Digestion with *Sal*I showed that the two Netherlands "whitepox" virus isolates (see Chapter 30) were identical with a strain of variola virus from Vellore, India, that had been handled in the laboratory at the time of their recovery—a pattern that was unique among 21 strains of variola virus examined (Dumbell & Kapsenberg, 1982).

Most of the data on DNA mapping illustrated in this chapter involve the use of the restriction endonuclease *Hin*dIII. Comparison of single strains of variola, vaccinia and monkeypox viruses using 5 other restriction endonucleases (*Bal*I, *Sma*I, *Kpn*I, *Sal*I and *Xho*I) confirmed the conclusions about their relationships derived from analyses with *Hin*dIII (Esposito & Knight, 1985).

Differences between the DNAs of Variola and Monkeypox Viruses

Because variola virus and monkeypox virus both cause a severe generalized poxvirus infection of man, special attention has been devoted to comparing their DNAs. Dumbell and his colleagues have used two techniques: fine structure mapping of equivalent *Hin*dIII fragments and analysis of heteroduplex formation, as revealed by electron microscopy.

Using the first method, Dumbell & Dollery (personal communication, 1984) have examined 7 corresponding cloned *Hin*dIII fragments of variola and monkeypox viruses, all derived from the central conserved position of the genome, with 20 restriction endonucleases. Their results are summarized in Table 2.5. There were between 2 and 6 (average 3.4) cleavage sites per kilobase pair (kbp), and the percentage of sites not shared varied, for different fragments, between 20% and 50% (average 30%).

Using similar cloned fragments of these two viruses, Kinchington et al. (1984) compared the threshold denaturation by formamide of homoduplexes and heteroduplexes. This method is sensitive and revealed a region of significant heterogeneity occurring in 4–6 kbp out of 43–45 kbp of the conserved region. The method has considerable potential and important conclusions can be expected to emerge from its further exploitation.

Genetic Studies

Because in recent years variola virus could be handled only in microbiologically highly secure laboratories, very few genetic studies have been carried out with it. However, as would be expected from the generality of recombination throughout the *Orthopoxvirus* genus (Woodroofe & Fenner, 1960), mixed infection of cells with variola virus and another orthopoxvirus was found to yield some hybrid progeny. Such progeny were obtained from mixed infections with rabbitpox and alastrim viruses (Bedson & Dumbell, 1964a) and cowpox and variola major viruses (Dumbell & Bedson, 1964; Bedson & Dumbell, 1964b). It was hoped that study of the latter might provide information on the origin of vaccinia virus.

By using the phenomenon of non-genetic reactivation (see above) and incubating inoculated eggs above the ceiling temperature of the active virus (variola minor or variola major viruses) many hybrid clones were obtained. These clones appeared to be stable in their biological characteristics; they showed a wide variety of combinations of properties, some being like those of one or other of the

Table 2.5. Comparisons of the cleavage sites produced by a battery of 20 restriction endonucleases in 7 matching *Hin*dIII fragments of variola and monkeypox viruses[a]

	Pairs of *Hin*dIII fragments (variola/monkeypox)						
	D/E	H/H	J/I	K/L	L/M	N/O	O/P
Length of fragment (kilobase pairs)	15.3	8.5	6.5	4.9	3.9	2.2	1.5
Number of restriction endonuclease cleavage sites per fragment	43	32	26	14	10	10	9
Cleavage sites per kilobase pair	2.8	3.8	4.0	2.9	2.6	4.5	6.0
Number of sites not shared	13	8	9	4	2	5	2
Percentage of sites not shared	30%	25%	35%	29%	20%	50%	22%

[a] From K. R. Dumbell & A. Dollery, personal communication (1984).

Table 2.6. Biological characteristics of cowpox and variola major viruses and of several hybrid clones derived from them[a]

Virus	Pock type[b]	A-type inclusion bodies	Diffusible LS antigen	"d" antigen[c]	Ceiling temperature (°C)	TTP sensitivity[d]	Plaque type	Plaques appear (day)	Skin lesions in rabbit[e]
Cowpox	RU	+	0	+	40	–	Trabeculated	2	+++
Variola major	WO	0	+	–	38.5	+	Rimmed	4	0
Hybrid viruses:									
VC2	IU	+	0	+	40	–	Trabeculated	2	+++
VC5	IU	0	0	+	38.5	–	Trabeculated	3	0
VC6	WO	+	0	–	40	–	Trabeculated	3	+
VC7	IU	+	0	+	40	+	Trabeculated	3	+++
VC8	WU	0	+	–	38.5	–	Rimmed	4	+
VC10	WU	+	0	–	39.5	–	Trabeculated	2	+
VC12	WU	+	0	–	40	–	Rimmed	3	+
VC13	IU	+	0	+	39	–	Trabeculated	2	+++
VC14	IU	+	0	+	40	–	Trabeculated	3	+++
VC16	WU	0	0	–	40	–	Trabeculated	2	+

[a] Based on Bedson & Dumbell (1964b).
[b] R = red, W = white, I = intermediate; U = ulcerated, O = non-ulcerated.
[c] Presence of "d" antigen (Rondle & Dumbell, 1982).
[d] Sensitivity of viral thymidine kinase to feedback inhibition by thymidine triphosphate (Bedson, 1982).
[e] +++ = large papule with haemorrhage and necrosis; + = small pink papule; 0 = insignificant lesion.

parental species, others being intermediate (Table 2.6).

Each of the 7 markers examined by Bedson & Dumbell (1964b), as well as sensitivity of the viral thymidine kinase to inhibition by thymidine triphosphate, studied later by Bedson (1982), and the presence of the "*d*" antigen (Rondle & Dumbell, 1982), was capable of segregating independently. The authors suggested that if enough hybrids were tested it would be possible to obtain one that resembled vaccinia virus in all these biological properties. However, it is unlikely that the restriction map of the DNA of such a virus would resemble that of vaccinia virus.

Species Diagnosis

The most useful biological characteristics for species diagnosis of variola virus are the production of small dense white pocks (0.3–0.6 mm in diameter) on the CA membrane, with a low ceiling temperature (37.5 °C for alastrim virus and 38.5 °C for all other strains), the low virulence for mice and chick embryos, the failure to grow in rabbit skin and the capacity to produce a cytopathic effect in pig embryo kidney cells and hyperplastic foci in HeLa cells. When these characteristics were found in material obtained from a case of suspected smallpox they constituted positive confirmation of the diagnosis; indeed, the recovery of typical variola virus pocks on the CA membrane was usually accepted as diagnostic.

It is worth noting, however, that combinations of properties rather like this are found with both camelpox virus and taterapox virus (Table 2.3). The source of the material usually removes any uncertainty; neither camelpox virus nor taterapox virus has ever been found to produce disease in man and variola virus has never been recovered from animals under conditions in which no suspicions arose of laboratory contamination (see Chapter 30). The 3 viruses can also be differentiated by laboratory tests:

(1) Only variola virus produces dense white pocks at all temperatures of incubation at which pocks develop.

(2) Variola virus produces hyperplastic foci and camelpox virus produces giant cells in several human and primate cell lines (Baxby, 1974).

(3) Taterapox virus is serially transmissible in rabbit skin (Gispen, 1972); variola virus is not.

(4) Taterapox virus is cytocidal for RK 13 cells, in which variola virus produces hyperplastic foci (Huq, 1972).

(5) Only variola virus produces a generalized disease in primates.

A definitive diagnosis of variola virus can be made by restriction endonuclease digestion of the viral DNA (see Fig. 2.6 and 2.9).

VACCINIA VIRUS

The vast bulk of experimental work on *Orthopoxvirus* as a genus and Poxviridae as a

family has been carried out on one species—vaccinia virus (see Holowczak, 1982; Fenner et al., 1987). It has also been used as a live virus vaccine more extensively, and for a much longer period, than any other immunizing agent.

Isolation from Natural Sources

The problem of the origin or origins of vaccinia virus is considered in Chapter 7. Here it is relevant to mention that the virus has been isolated from skin lesions of several species of domestic animals (Table 2.7). During periods when vaccination of humans against smallpox was being vigorously pursued there were clearly numerous opportunities for infection to be transferred from recently vaccinated persons to various domestic animals, with subsequent spread in herds either by milkers acting as vectors or by some other route.

Some cases of "cowpox" in cattle (Dekking, 1964; Dahaby et al., 1966; Maltseva et al., 1966; Topciu et al., 1976) and of "camelpox" in camels (Krupenko, 1972) have been caused by vaccinia virus. It is likely that all cases of buffalopox (Lal & Singh, 1977), in both Egypt and India, were caused by vaccinia virus. Although one strain of "buffalopox" virus had a ceiling temperature of 38.5 °C (Baxby & Hill, 1971), it had the DNA map of vaccinia virus (K.R. Dumbell, personal communication, 1983). As recently as 1986, buffalopox has been reported from several areas in central India. Four isolates recovered from infected buffaloes were shown by *Hin*dIII electropherograms to be strains of vaccinia virus (K. R. Dumbell, personal communication, 1986).

Rabbitpox virus warrants particular mention, since it has been extensively used in studies of pathogenesis and orthopoxvirus genetics, including the construction of the first DNA map of vaccinia virus. The name was first given to a strain of vaccinia virus that caused severe epidemics in laboratory rabbit colonies in New York in 1933–1934 (Greene, 1933; Rosahn & Hu, 1935). Subsequently, a similar virus of high virulence for rabbits was recovered from a colony of rabbits in Utrecht, Netherlands, under conditions which were said to preclude the infection of the animals with vaccinia virus (Jansen, 1946). Both would be classified as "neurovaccinia", in that they are highly virulent by intracerebral injection in rabbits and produce ulcerated haemorrhagic pocks on the CA membrane.

Two viruses recovered in unusual circumstances in central and western Africa, termed "MK-10-73" and "Lenny" respectively, were proved by DNA mapping to be strains of vaccinia virus with a lower ceiling temperature (39.5 °C and 38.5 °C respectively) than standard strains (41 °C) (K.R. Dumbell, personal communication, 1984). MK-10-73, said to have been isolated from the kidney of a wild monkey captured in Zaire, was processed in Moscow (Shelukhina et al., 1975). "Lenny" was recovered from a severely malnourished Nigerian woman who died after an illness with fever and a generalized rash that was very like eczema vaccinatum (Bourke & Dumbell, 1972). The origin of these strains is obscure. Temperature-sensitive (*ts*) mutants of vaccinia virus are readily obtainable in the laboratory (Chernos et al., 1978; Dales et al., 1978; Sambrook et al., 1966). Contamination at some stage cannot be excluded with MK-10-73. "Lenny" resembles the Wyeth strain of vaccinia virus, then being used for vaccination in Nigeria, in all biological properties except the ceiling temperature (K.R. Dumbell, personal communication, 1984); presumably it was a naturally occurring *ts* mutant, perhaps selected by the unusual conditions under which it grew (it was obtained 16 days after the rash appeared).

Table 2.7. Animals from which vaccinia virus has been recovered (infection from human sources always possible)

Animal source	Illustrative reference
Buffalo (buffalopox)	Baxby & Hill (1971); Lal & Singh (1977)
Camel	Krupenko (1972)
Cow	Dahaby et al. (1966); Dekking (1964)
Monkey (MK-10-73)[a]	Shelukhina et al. (1975)
Pig	Maltseva et al. (1966)
Rabbit (rabbitpox)	Jansen (1946); Rosahn & Hu (1935)

[a] Possibly a contaminant, from the field (Zaire) or in the laboratory.

The Variability of Strains and their Pathogenicity

In sharp contrast to variola virus, which has a narrow host range, vaccinia virus has a very wide host range and grows rapidly and to high titre in many species of animals and in most kinds of cultured cells. In chick embryos,

it produces large pocks on the CA membrane within 48 hours, whereas other orthopoxviruses produce smaller pocks and take 3 days to reach the optimum size for pock counts.

Neurovaccinia and dermal vaccinia

Two terms occur in older works on vaccinia virus that need some explanation: "dermal vaccinia" and "neurovaccinia". Early workers usually maintained vaccinia virus by passage through calves, sheep or rabbits, the animals usually being inoculated by scarification (see van Rooyen & Rhodes, 1948). When the skin lesions reached a sufficient size the infected skin area was scraped, the material thus obtained being called "dermal vaccinia" or "dermovaccine". Strains of vaccinia virus that were maintained by intracerebral inoculation of rabbits, sometimes with occasional testicular passage (Levaditi et al., 1922, 1938), were called "neurovaccinia".

Differences between strains of vaccinia virus

Two systematic studies have been made of the biological characteristics of various laboratory strains of vaccinia virus (Fenner, 1958; Ghendon & Chernos, 1964). A variety of differences were found, involving the production of haemagglutinin, heat resistance of the virion, pathogenicity in rabbits and mice (Fenner, 1958; Table 2.8), and plaque morphology and virulence for monkeys (Ghendon & Chernos, 1964). The traditional division of strains into "dermovaccine" and "neurovaccine" broadly differentiated viruses of lower and higher virulence for the laboratory animals used; in particular, the occurrence of haemorrhagic pocks on the CA membrane was correlated with the production of large indurated skin lesions with a purple centre following the intradermal inoculation of rabbits. White pock mutants of the "neurovaccine" strains produced small pink nodules in the rabbit skin.

Some strains or mutants of vaccinia virus fail to produce haemagglutinin. Rabbitpox virus (Utrecht strain) is one example (Fenner, 1958). Another HA^- mutant (IHD-W) produces a non-glycosylated form of the 89 000 molecular weight polypeptide, the glycosylated form of which Payne (1979) identified as the haemagglutinin. As with rabbitpox virus, infection with the mutant did not evoke the production of haemagglutinin-inhibiting antibodies, suggesting that glycosylation must produce an important conformational change in the secondary structure of the polypeptide.

Differences in DNAs of different strains of vaccinia virus

In spite of this variability in biological characteristics, all strains of vaccinia virus that have been examined have remarkably similar DNAs, as judged by restriction endonuclease analysis. Fig. 2.10 illustrates the similarity between the DNAs of 5 strains of vaccinia virus and their difference from variola and monkeypox DNAs, using three restriction endonucleases. The vaccinia strains compared included a classical "neurovaccinia" strain (rabbitpox Utrecht) and two classical dermal strains (LS and HI).

Variation within a Strain

Several investigators have shown that uncloned stocks of most orthopoxviruses are in

Table 2.8. Some biological characteristics of several different laboratory strains of vaccinia virus[a]

Strain	Pock type[b]	Haemagglutinin production	Heat resistance of infectivity	Virulence after intracerebral inoculation		Skin lesions in rabbit[c]
				Mouse	Rabbit	
Gillard	WO	+	High	−	−	+
Connaught	WO	+	High	−	−	+
Mill Hill	WO	+	High	+	−	+
Lederle-7N	WO	+	Low	−	−	+
Nelson	WO	+	Moderate	++	−	0
Williamsport	WO	+	High	++	++	+
Pasteur	WU	+	High	+	++	+++
IHD	RU	+	High	+++	+++	+++
Rabbitpox-U	RU	−	High	+++	+++	+++
Rabbitpox-RI	RU	+	High	+++	−	+++

[a] From Fenner (1958).
[b] R = red; W = white; U = ulcerated; O = non-ulcerated.
[c] +++ = large papule with haemorrhage and necrosis; + = small papule; 0 = insignificant lesion.

fact mixtures of genetically dissimilar virions. For example, since orthopoxviruses which produce haemorrhagic pocks yield, on cloning, a substantial proportion of white non-ulcerated pocks (varying between 0.01% and 1%, according to species; Gemmell & Fenner, 1960; Dumbell & Archard, 1980), stock preparations of those viruses must contain several different white pock mutants.

Using other methods of assay, stocks of vaccinia virus which appear to be homogeneous with respect to the type of pock produced can sometimes be shown to be mixed, either in the plaques produced on selected kinds of cells (Ghendon & Chernos, 1964) or by heterogeneity in the patterns produced on analysis with restriction enzymes (Wittek et al., 1978).

Genetic Studies

Genetic recombination occurs when single cells are co-infected with two strains of virus with several different marker properties. Early experiments on recombination (Fenner, 1959) utilized a "dermal" and a neurovaccinia strain (rabbitpox). Subsequently, the observation that all vaccinia strains producing ulcerated haemorrhagic pocks on the CA membrane yielded white pock mutants (Fenner, 1958) led to the demonstration of recombination between some of these mutants but not others (Gemmell & Fenner, 1960). Certain white pock mutants were shown to be host-cell-restricted conditional lethal mutants (Fenner & Sambrook, 1966). Unlike the wild-type virus and some of the white pock mutants, they failed to replicate in pig kidney cells. Subsequent studies (Lake & Cooper, 1980) showed that the pig-kidney-cell-restricted mutants had deletions at the left-hand terminus and the white pock mutants that grew in pig kidney cells had deletions at the right-hand terminus of the rabbitpox virus genome. Although segments of DNA were lost in the terminal deletions, the changes were not always simple deletions; terminal sequence duplication and transposition were also involved (Moyer et al., 1980).

Suites of temperature-sensitive conditional lethal mutants of rabbitpox and vaccinia viruses have also been assembled (Sambrook et al., 1966; Padgett & Tomkins, 1968; Chernos et al., 1978) and have been employed in experiments on the biogenesis of vaccinia virus (Dales et al., 1978).

A new era in poxvirus genetics began when fragments of vaccinia virus DNA obtained after digestion with restriction endonucleases were cloned in *Escherichia coli* (Wittek et al., 1980). The whole genomes of several strains of cowpox, vaccinia and variola viruses have now been cloned, and detailed analysis of the structure and function of poxvirus DNA has begun. In other experiments based on cloned viral DNA, fragments of foreign DNA have been incorporated into the vaccinia virus genome and expressed during infection (Smith et al., 1983). This opens up the possibility that after suitable genetic manipulation vaccinia virus may be used for the vaccination of humans or domestic animals against diseases caused by a variety of infectious agents other than orthopoxviruses (Quinnan, 1985).

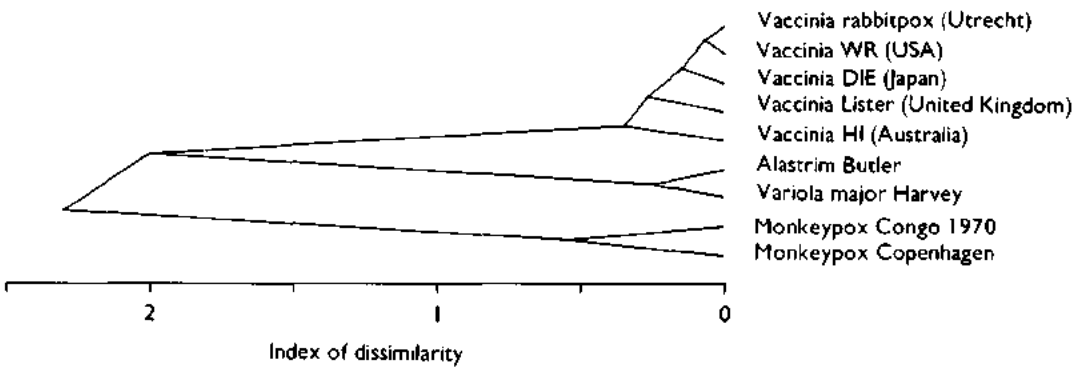


Fig. 2.10. Dendrogram illustrating the similarities and differences between *HindIII*, *SmaI*, and *XhoI* cleavage sites on DNAs from 5 vaccinia strains originating in different countries, compared with 2 monkeypox and 2 variola DNAs (see legend of Fig. 2.7). Number of attributes = 66. Full details of the origins of the viral strains are given in Esposito & Knight (1985), from which the data on restriction sites were derived.

Species Diagnosis

As illustrated in Fig. 2.7 and in more detail by Mackett & Archard (1979), the genome of vaccinia virus is distinctive, and comparison of DNA maps provides conclusive evidence whether any isolate under examination belongs to this species. Biological characteristics that are particularly useful for diagnostic purposes are the rapid growth of large pocks on the CA membrane, which may vary from haemorrhagic to dense white in appearance, the high ceiling temperature of growth on the CA membrane (41 °C or higher) and the broad host range.

COWPOX VIRUS

Cowpox virus is of interest in the context of smallpox eradication because of its historic involvement in the discovery of vaccination (see Chapter 6) and because it is transmissible to man (see Chapter 29). Research over the last decade has shown that there is a large number of somewhat similar viruses which can cause infections in a variety of animals, rodents probably being the reservoir hosts (see Chapter 29). In this book all these viruses are included within the cowpox virus species.

Cowpox and Horsepox in Europe

The occurrence of a sporadic pox disease of cows transmissible to man had been known for centuries and was brought to public attention by the observations of Jenner. The distinctive character of the usual cause of cowpox—the *Orthopoxvirus* species now categorized as "cowpox virus"—was first recognized by Downie (1939a,b). Other causes of what is called "cowpox" are vaccinia virus, usually derived from a human source, and a species of *Parapoxvirus* that causes milker's nodules in man. The last-named virus was one of the causes of Jenner's "spurious cowpox". It is only the first of these 3 viruses with which we are concerned here.

"Horsepox" is a tantalizing disease for a modern virologist who is interested in the history of Jenner's vaccine. Jenner confused the situation by suggesting that cowpox in cows usually originated from "grease" of horses—a lesion of the fetlocks (Plate 2.15A) that may be caused by several different agents, most commonly the bacterium *Dermatophilus congolensis* (Gillespie & Timoney, 1981). During the 19th century, a poxvirus ("horsepox virus") was an occasional cause of this syndrome. Loy (1801) demonstrated that material from such a lesion produced cowpox when inoculated in cows' teats, and he protected a child from challenge variolation by "equination". Usually, according to Crookshank (1889), horsepox was associated with pustular lesions on the perineum or the head of the horse (Plate 2.15B), as well as sometimes on the fetlocks (grease). Both Chaveau (cited by Crookshank, 1889) and Fleming (1880) believed that horsepox was due to the accidental infection of horses with cowpox virus. Evidence now available suggests that both cowpox and in the past at least some cases of horsepox were due to the incidental infection of these animals by cowpox virus, which probably circulates in rodents; or, as Jenner suggested, it may have been transferred accidentally from horses to cows, or vice versa, by man. More recently horsepox, like "cowpox", has been produced by the infection of horses with vaccinia virus originating from vaccinated human subjects (Kii & Ando, 1937). Finally, Baxby (1981) has suggested that horsepox, which he postulates was a disease distinct from the infection of horses with cowpox virus, and which became extinct at about the end of the 19th century, was in fact caused by vaccinia virus.

Genetic Studies

White pock mutants, which have been important for genetic studies of orthopoxviruses and in speculations about the evolution of both vaccinia and variola viruses, were first recognized in experiments with cowpox virus inoculated on the CA membrane (Downie & Haddock, 1952; Tongeren, 1952). Early attempts to exploit this system for genetic studies of cowpox virus were frustrated by the failure to obtain recombination between many combinations of separately isolated mutants derived from the Brighton strain of cowpox virus (Dumbell, unpublished results, 1960; Greenland & Fenner, unpublished results, 1960). This failure was explained by the discovery that all white pock mutants of the Brighton strain involved substantial deletions from the right-hand end of the genome (Archard & Mackett, 1979).

Amano et al. (1979) found that all white pock mutants of cowpox virus failed to

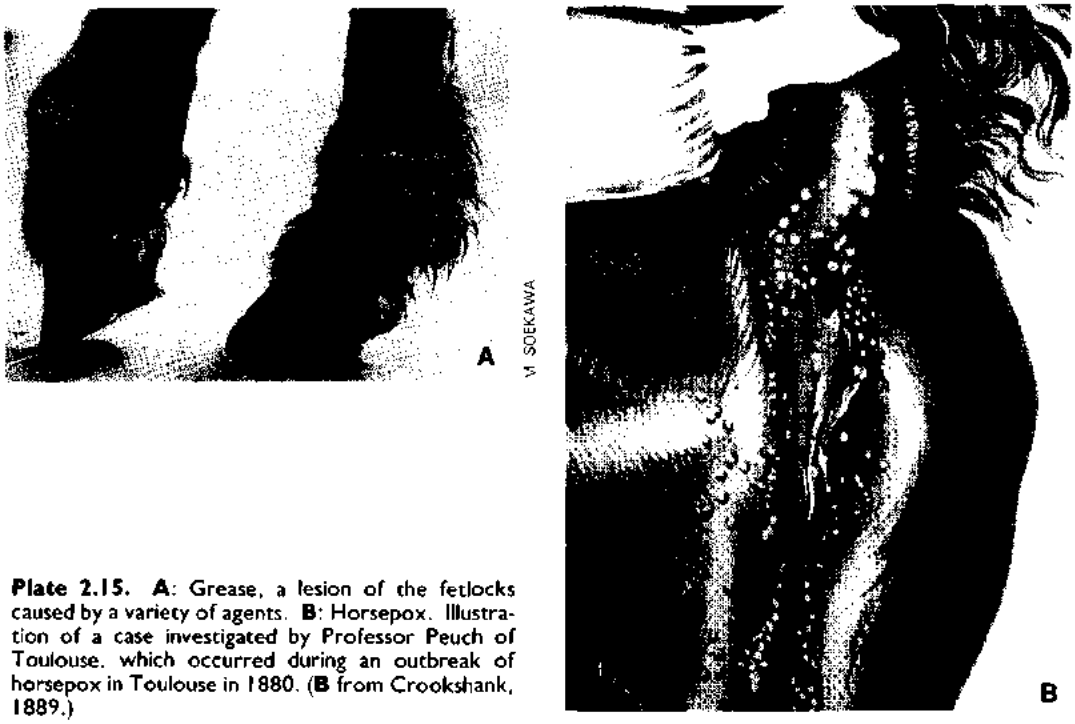


Plate 2.15. **A**: Grease, a lesion of the fetlocks caused by a variety of agents. **B**: Horsepox. Illustration of a case investigated by Professor Peuch of Toulouse, which occurred during an outbreak of horsepox in Toulouse in 1880. (**B** from Crookshank, 1889.)

produce an early cell-surface antigen that was produced in infected cells by all the parental strains (10 wild-type and 28 white pock mutants were investigated). Rondle & Dumbell (1962) showed that another antigen, "*d*", which was present in extracts of cells infected with wild-type cowpox virus did not occur in its white pock mutants. Subsequently, Rondle & Dumbell (1982) demonstrated that "*d*" antigen occurred in several orthopoxviruses that produced necrotic haemorrhagic lesions after intradermal inoculation in rabbits (cowpox virus, neurovaccinia strains including rabbitpox virus, and certain recombinants between cowpox and variola viruses), but not in those that did not produce such lesions (cowpox white mutants, variola and some recombinants between variola and cowpox viruses—see Table 2.6).

Species Diagnosis

The most reliable biological indicators of cowpox virus are the production of large haemorrhagic pocks on the CA membrane, with a ceiling temperature of 39 °C, the production of a large haemorrhagic lesion after intradermal inoculation in rabbits, the wide host range, and the production of A-type as well as B-type inclusion bodies in infected cells. Although there is greater variability between the DNA maps of different strains of cowpox virus (using the broad definition adopted here) than is the case with other species of *Orthopoxvirus* (see Chapter 29; Fig. 29.4), all strains of cowpox virus cluster together in the dendrogram and can be readily differentiated from other orthopoxviruses.

LABORATORY CONFIRMATION OF SMALLPOX DIAGNOSIS

Laboratory methods played a crucial role in the global smallpox eradication campaign; indeed the achievement of eradication could not have been confidently certified without their use. The development of laboratory support for the Intensified Smallpox Eradication Programme is outlined in Chapter 10. The laboratory also provided support for the clinical diagnosis of smallpox. This was not of much importance in endemic countries when smallpox was a common disease, but was of great value in non-endemic countries confronted with suspected imported cases (Mac-

rae, 1982) and in the endemic countries as eradication approached (Ježek et al., 1978f).

Preparation of a Guide for Laboratory Diagnosis

In October 1967 a WHO Scientific Group on Smallpox Eradication met in Geneva. Among other recommendations, it proposed that laboratories for diagnosis should be developed in each of the larger countries and regional laboratories should be designated to serve groups of smaller countries (WHO Scientific Group on Smallpox Eradication, 1968). In April 1968 a group of experts met in Philadelphia, USA, to commence the preparation of a manual, *Guide to the Laboratory Diagnosis of Smallpox for Smallpox Eradication Programmes*, which was intended to provide information on procedures that could be performed in the surveillance activities of smallpox eradication programmes in endemic areas.

The guide, which incorporated the comments of a number of other experts, was published in 1969 (World Health Organization, 1969a). It described methods of specimen collection, microscopic examination of smears (by the method of Gispen, 1952), precipitation in gel, isolation of virus on the CA membrane, the maintenance of records and the layout of a smallpox diagnostic laboratory (see Chapter 30, Fig. 30.3A). In retrospect, the value of the guide can be assessed by a review of the changes that occurred as the eradication programme proceeded.

(1) Examination of stained smears was not widely practised, and in developed countries this method was completely displaced by electron microscopic examination of negatively stained preparations.

(2) The guide facilitated the development of national diagnostic laboratories in some heavily populated countries, such as India and Bangladesh. As eradication approached in these countries, duplicate specimens were sent to the WHO collaborating centres (see Chapters 15 and 16).

(3) The concept of a regional laboratory network did not materialize; instead reliance was placed on the services of the WHO collaborating centres in Moscow, USSR, and Atlanta, USA.

(4) A special kit was later developed for the collection and dispatch of specimens (see Chapter 10, Plate 10.6).

Methods of Laboratory Diagnosis

Laboratory diagnostic methods used can be divided into three groups: those involving the recognition of virions or of viral antigens in material collected from the patient, and inoculation of the virus in laboratory animals (including the CA membrane) or cultured cells. Subclinical infection with variola virus or the retrospective diagnosis of human monkeypox could be recognized only by serological tests (see Chapters 1, 3 and 29). Detailed descriptions of techniques are given by Downie & Kempe (1969) and Nakano (1979, 1982).

Methods involving the recognition of virions

Staining for light microscopy. In smallpox, virions occurred in vast numbers in the vesicle fluid and in pustules and scabs, and pathologists developed a variety of staining methods which made it possible to see the virions in stained smears. Paschen's method (Paschen, 1906), using basic fuchsin, which stained the virions deep red, was probably the most widely used (see Plate 2.1); it was subsequently replaced by silver impregnation techniques (Morosow, 1926; Gispen, 1952). Gispen's method was advocated in the aforementioned WHO *Guide to the Laboratory Diagnosis of Smallpox for Smallpox Eradication Programmes* (World Health Organization, 1969a) as the method of choice for the presumptive diagnosis of smallpox. In skilled hands it was a useful test but was open to misinterpretation by those not familiar with the technique—especially after the lesions became pustular—and it was not widely used.

Electron microscopy. Nagler & Rake (1948) were the first to employ electron microscopy for the diagnosis of smallpox, using shadow-cast preparations of crusts or vesicle fluid that had previously been purified and concentrated by centrifugation. However, widespread use of electron microscopy as a diagnostic method was not feasible until the negative staining technique was introduced by Brenner & Horne in 1959. Peters et al. (1962) and subsequently Cruickshank et al. (1966) showed the value of this method for recognizing poxvirus or herpesvirus particles in vesicle fluid and scabs taken directly from patients. Like the examination of stained smears, electron microscopy could not be used to distinguish between variola, vaccinia and monkeypox viruses, which are morphologi-

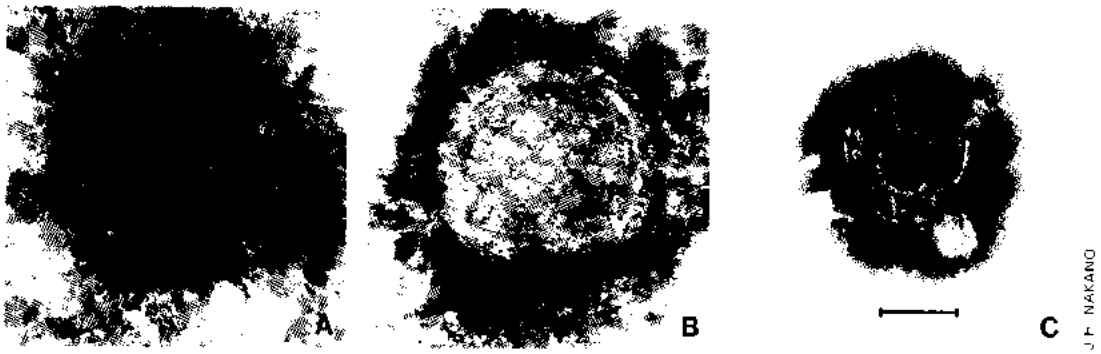


Plate 2.16. Virions of variola virus (**A** and **B**) and varicella virus (**C**) as seen in negatively stained preparations submitted for diagnosis to the WHO Collaborating Centre at the Centers for Disease Control, Atlanta, GA, USA. Bar = 100 nm.

cally indistinguishable, but it was of great value in confirming or possibly excluding poxvirus infection and in distinguishing between poxvirus infection and chickenpox. In 1971 it became an integral part of the diagnostic procedures used by the WHO collaborating centres in Atlanta, USA, and Moscow, USSR. Plate 2.16 shows typical virions of variola virus along with those of herpesvirus (from a patient with chickenpox), as seen in negatively stained specimens of crusts, scrapings or vesicle fluid.

Methods involving the recognition of viral antigens

Initially, complement-fixation and flocculation tests were used for the demonstration of orthopoxvirus antigens in vesicle or pustule fluid, the former test being considered preferable (Craigie & Wishart, 1936; Downie, 1946). Subsequently, gel precipitation was developed, and an adaptation of this method on microscope slides was described in detail in the WHO guide. This technique was extensively employed in some national campaigns (e.g., in India; Ježek et al., 1978f) in laboratories that did not have an electron microscope available for rapid diagnosis. With adequate amounts of recently collected antigen it was a quick and accurate test (Rao et al., 1970; A.W. Downie, personal communication, 1981).

Other serological tests for viral antigen were sometimes used but never became widely popular. Kitamura et al. (1977a) suggested that direct immunofluorescence could be used for rapid diagnosis in the field, but they and other workers (Tarantola et al., 1981) recorded a number of false positive results, a major disadvantage as the achievement of eradication approached.

Tests in animals and isolation of the virus

All the methods described so far had the limitation that, if positive, they did not distinguish between different orthopoxviruses. This drawback was of little significance when smallpox was a common disease, but it became increasingly important as eradication proceeded, particularly after human monkeypox was recognized in 1970.

In the early days of virology the only animal diagnostic procedure useful in distinguishing variola virus from varicella virus was the inoculation of monkeys, clearly a method that could not be widely used. Paul's test, which involved the scarification of the rabbit cornea, provided a more widely applicable method, but according to Downie (1946) and Marennikova et al. (1961), it often gave false negative results. However, variola virus produced very characteristic pocks on the CA membrane, which provided a simple and reliable laboratory method for isolating and recognizing that virus.

Production of pocks on the CA membrane. It had been known since the 1930s that orthopoxviruses grew on the CA membrane of developing chick embryos, and that when dilute suspensions were used different strains of vaccinia virus produced characteristic pocks. Although others had cultivated variola virus on the CA membrane, Downie & Dumbell (1947b) were the first to demonstrate the reproducible and clear-cut differences between the pocks produced by variola virus and those due to vaccinia virus. CA membrane inoculation soon became the method of choice for the isolation of variola virus (World Health Organization, 1969a). The pocks produced by variola virus are quite

distinctive and can be readily distinguished from those produced by the other orthopoxviruses that are pathogenic for man—vaccinia, cowpox and monkeypox viruses (see Plate 2.5). It has remained the method of choice for the preliminary identification of orthopoxviruses, and it was the fact that the pock morphology of monkeypox virus was different from that of variola virus that led Marennikova et al. (1972a) to make the first laboratory diagnosis of human monkeypox.

Isolation in cultured cells. Most human and non-human primate cells, and some cells derived from other species (rabbit kidney and pig embryo kidney cells), are susceptible to infection with variola virus. In most cell systems variola virus causes cell fusion and multinucleated foci; the small (1–3 mm in diameter) hyperplastic foci are quite distinctive when compared with the large (2–6 mm in diameter) plaques produced by vaccinia, monkeypox and cowpox viruses (Kitamura, 1968; see Plate 2.13). Pig embryo kidney cells are unusual in that variola virus, which has a narrow host range, produces a cytopathic effect, whereas most strains of monkeypox virus, which has a wide host range, do not (Marennikova et al., 1971).

Although cell culture was sometimes more sensitive (Nakano, 1979), inoculation on the CA membrane was generally a more useful test with field material, since positive results could be obtained even with scabs that were contaminated with bacteria (Sarkar & Mitra, 1963), which usually destroyed cell cultures. Also, if the content of viable virus was low it often took several days, and perhaps serial passage, before characteristic lesions occurred in cultured cells, whereas a result could always be obtained within 3 days by CA membrane inoculation.

Differentiation between orthopoxviruses. Four species of *Orthopoxvirus* can produce lesions in man: variola, monkeypox, vaccinia and cowpox (see Chapter 29). Each produces distinctive pocks on the CA membrane; in addition, the 4 species can be differentiated by several other biological properties (Table 2.9) as well as by restriction endonuclease mapping of their DNAs.

Comparison of Different Laboratory Diagnostic Methods

Noble et al. (1970) assessed the value of various laboratory procedures for the diagnosis of variola minor in Brazil. They always

1974

1970

Plate 2.17. *Left:* Svetlana S. Marennikova (b. 1923). A leading Soviet expert on orthopoxviruses and Chief of the WHO Collaborating Centre on Smallpox and other Related Infections established at the Moscow Research Institute for Viral Preparations in 1966. She was responsible for the laboratory diagnosis of the first recognized case of human monkeypox and for much research on smallpox vaccine, diagnostic methods and the immunology and biology of orthopoxviruses. Dr Marennikova participated in all the meetings of WHO expert groups on smallpox from 1964 onwards and was elected vice-chairman of several. She was also a member of a number of international commissions and of the Global Commission. *Right:* Emma M. Shelukhina (b. 1929). A staff member of the WHO Collaborating Centre at the Moscow Research Institute for Viral Preparations. She collaborated in diagnostic work and research on smallpox and other orthopoxviruses and was a WHO consultant in India and Pakistan.

Table 2.9. Biological characteristics used in diagnostic laboratories to differentiate between orthopoxviruses that infect man[a]

Characteristic	Virus			
	Variola	Vaccinia	Monkeypox	Cowpox
Pock on CA membrane	Small opaque white	Strains vary; large opaque white or ulcerated	Small ulcerated at 35 °C	Large, bright red, haemorrhagic
Ceiling temperature	37.5–38.5 °C	41 °C	39 °C	40 °C
Skin lesion after intradermal inoculation of rabbit	Nil or small nodule, non-transmissible	Strains vary; indurated, sometimes haemorrhagic nodule	Large, indurated haemorrhagic nodule	Large, indurated haemorrhagic nodule
Growth in pig embryo kidney cells	+	+	–	+

[a] Unequivocal diagnosis of all these species can be made by the examination of electropherograms produced after restriction endonuclease digestion of viral DNAs.

obtained positive results with both scabs and vesicular or pustular fluid stored in capillary tubes and tested by electron microscopy and cultivation on the CA membrane; a few such specimens were negative by gel precipitation. They were less successful with material that had been stored as smears on glass slides for up to 2 months at room temperature. In searches with the electron microscope for a maximum period of 10 minutes for each specimen, only 30 out of 52 (58%) were positive. Some of these showed structural degeneration of the virus particles; presumably this had proceeded so far on those diagnosed as negative that no intact virions could be found during the 10-minute search. Twenty-seven out of the 30 specimens found positive by electron microscopy yielded virus when inoculated on the CA membrane; 1 specimen found negative by electron microscopy was positive on CA membrane inoculation. Positive culture was never obtained by serial passage of membranes that appeared normal; occasionally membranes that had cloudy or non-diagnostic opacities on first inoculation showed unequivocal variola virus pocks on the second passage. Only 41% of the stored smears were positive by gel diffusion.

The most comprehensive analysis of the laboratory diagnosis of smallpox was reported by Nakano (1973), who kindly updated the figures in 1982 to show the situation at that time (Table 2.10). The material under study had been shipped to the Centers for Disease Control, Atlanta, USA, from Africa, South America and Asia and had usually been in transit for between 2 and 4 weeks, and occasionally longer, often at high ambient temperatures. Four methods were used: electron microscopy, gel precipitation, and cultivation on the CA membrane and in Vero cells. By March 1981 a total of 6919 specimens had been examined, many of them from suspected chickenpox cases during precertification testing in Ethiopia and Somalia. Of the 981 positive specimens, 940 were identified as

Table 2.10. Relative efficiency of 4 laboratory methods for diagnosing variola or human monkeypox infections. Tests on material from vesicles or scabs in 981 positive specimens from 6919 cases of suspected smallpox or monkeypox, accumulated between January 1966 and March 1981[a,b]

Method	Specimens positive for poxvirus by any one method or more		Specimens positive for poxvirus by			
			EM	CAM	AG	TC
	Variola	Monkeypox[c]				
EM + CAM	940	41	967 (98.6%)	870 (88.7%)	–	–
EM + CAM + AG	906	30	922 (98.5%)	833 (89.0%)	678 (72.4%)	–
EM + CAM + AG + TC	179	7	182 (97.8%)	117 (62.9%)	117 (62.9%)	135 (72.6%)

[a] J.H. Nakano (personal communication, 1982).

[b] The low percentage (14%) of positive results was due to the inclusion of material from large numbers of cases of chickenpox sampled during the late stages of the eradication campaigns in Ethiopia and Somalia.

[c] 1970 to end of March 1981.

EM = electron microscopy; CAM = egg inoculation on CA membrane; AG = gel-precipitation test; TC = tissue culture inoculation.

variola virus and 41 as human monkeypox virus.

Electron microscopy had the advantage of being much the most rapid method of making a presumptive diagnosis, which was a very important requirement, especially in non-endemic countries. In scabs or material that had been some time in transit, it was also the most sensitive, although fields might have to be searched for as long as 30 minutes before a specimen was declared negative. The longer period of search undoubtedly accounted for the greater percentage of successes recorded by Nakano with stored specimens, compared with the experience of Noble et al. (1970). Inoculation on the CA membrane had the great advantage of allowing differentiation between the 4 orthopoxviruses that can infect man (variola, monkeypox, cowpox and vaccinia viruses). It was also the most sensitive with fresh specimens of vesicular fluid, since one infectious particle was potentially capable of producing a pock. Positive results were obtained on the CA membrane with 14 specimens that were negative by electron microscopy, whereas 97 specimens were positive by electron microscopy but negative by CA membrane inoculation. However, Nakano (1979) found that the susceptibility of the CA membrane, although usually quite satisfactory, was sometimes unacceptably low, as judged by control inoculation in cultured cells. For this reason he found it useful to make inoculations on cultured cells, especially with critical specimens in which recovery of the responsible virus was very desirable (e.g., in suspected human monkeypox). Out of 186 specimens that were tested by all 4 methods, 182 were positive by electron microscopy, 135 by tissue culture inoculation and 117 by CA membrane inoculation—i.e., 18 specimens were positive by tissue culture but negative on the CA membrane. Growth in pig embryo kidney cells was sometimes used to differentiate between variola and monkeypox viruses. Nakano confirmed the finding of Noble et al. (1970) that gel precipitation was the least sensitive technique and that it was often negative in lesion material that had been exposed to ambient temperatures for several days.

Tests for Species-Specific Viral Antibodies

Most serological tests for orthopoxvirus antibodies were positive in the late stages of smallpox, except in some cases of haemorrhagic-type smallpox, which were in any case fatal, but the detection of antibodies was irrelevant for the ordinary laboratory diagnosis of smallpox. However, serological tests were useful in determining whether certain patients who had recovered from a febrile illness associated with a rash had suffered from smallpox. They provided the only way of diagnosing variola sine eruptione and subclinical infections, the complement-fixation test being particularly valuable because of the short period after infection that it remained positive (see Chapter 1).

Serological tests were important in another context—namely, the specific diagnosis of prior infection with monkeypox virus, whether in humans or in animals (see Chapter 29). Several attempts were made to develop methods for differentiating between antibodies due to prior infection with variola, monkeypox and, in certain cases, other orthopoxviruses (see Chapter 3). The methods described depended on the multiple absorption of positive sera and the recognition of antibody to a particular viral species after such absorption. Immunoprecipitation (Gispen & Brand-Saathof, 1974) and immunofluorescence (Gispen et al., 1974) were used to differentiate antibodies due to infection with variola, monkeypox and vaccinia viruses. Subsequently, Hutchinson et al. (1977) and Marennikova et al. (1981) developed absorption tests for detecting specific antibodies using radioimmunoassay and ELISA respectively. All these methods required that adequate amounts of relatively potent serum should be available for testing, and the requisite multiple absorptions were tedious and time-consuming. However, they were useful in providing evidence of past monkeypox virus infection in man and in certain species of monkeys and squirrels.

RESISTANCE TO PHYSICAL AND CHEMICAL AGENTS

The infectivity of orthopoxviruses is in general relatively unaffected by environmental conditions, compared with that of many other viruses. The focus of work on the resistance of vaccinia and variola viruses to physical and chemical agents was quite different: with vaccinia virus the practical objectives were either to ensure the viability and potency of stored vaccine preparations or to

produce an effective inactivated vaccine; with variola virus interest was centred on epidemiological parameters such as its viability in droplet nuclei and the persistence of infectivity in scabs and on fomites.

Vaccinia Virus

The heat resistance of vaccinia virus, prepared in various ways and exposed to different temperatures, was of major importance in the development of efficient vaccination programmes (see Chapter 11). Glycerolated liquid vaccine, while relatively stable at refrigerator temperature for a few weeks, was quickly inactivated at higher temperatures, especially if exposed to sunlight.

Kaplan (1958) studied the inactivation of vaccinia virus at various temperatures ranging from 50 °C to 60 °C. There was an initial rapid fall in infectivity to 10^{-5} or 10^{-6} of the original titre, followed by inactivation of the residual virus at a much slower rate. Perhaps this phenomenon provides an explanation for the successful long-distance transportation of vaccinia virus that took place from time to time during the 19th century (see Chapter 6). The persistent infectivity was not due to the selection of genetically resistant virus, but was shown by Woodroofe (1960) to be attributable to some change that occurred during the storage of concentrated preparations of virus in the liquid state. The infectivity of freshly prepared suspensions of partially purified vaccinia virions suspended in McIlvaine's buffer was completely destroyed within 60 minutes at 55 °C and within 90 minutes at 50 °C.

Camus (1909), working in France, and later Otten (1927) in Batavia (Jakarta) showed that crude vaccine dried slowly *in vacuo* over sulfuric acid, and stored *in vacuo*, was much more stable than liquid vaccine. Such preparations were used in the French colonies in Africa and for the elimination of smallpox in the Netherlands East Indies (Indonesia) in the late 1930s (see Chapter 8). However, the material was difficult to reconstitute, it was often heavily contaminated with bacteria, and there was a good deal of variation between batches. Subsequently, freeze-drying, which had long been used on a laboratory scale for preserving and transporting viruses and bacteria, was developed on a commercial scale for smallpox vaccine (see Chapter 7). Such material was very stable; Kaplan (1969) reported that an early production batch of freeze-dried vaccine withstood storage at 45 °C for at least 6 years without loss of potency.

Other methods of inactivation of vaccinia virus were relevant mainly in relation to efforts to produce an inactivated virus vaccine (Turner et al., 1970; see Chapters 3 and 7). Most workers found heating to be unsuitable, as it destroyed antigenicity. Other methods of inactivation that were investigated included ultraviolet irradiation, which had the disadvantage that a small overdosage severely damaged antigenicity (Kaplan, 1969), and formaldehyde, which also damaged antigenicity (Amies, 1961). Photodynamic inactivation with methylene blue (Turner & Kaplan, 1968) and gamma irradiation (Marennikova & Macevič, 1975) appeared to inactivate infectivity with little effect on antigenicity.

Variola Virus

Periodic assays showed that in temperate climates smallpox scabs could retain infectivity at room temperature for several years. Downie & Dumbell (1947a) recovered variola major virus from crusts stored at room temperature, in the dark or in daylight, for up to 1 year; Wolff & Croon (1968) recorded the persistence of viable alastrim virus in scabs kept in envelopes in a laboratory cupboard for over 13 years. The potential significance of these findings in relation to a possible return of smallpox is discussed in Chapter 30; of more immediate concern to the smallpox eradication programme was the degree to which viability might persist in some tropical countries in which variolation was still practised during the 1970s. Huq (1976) investigated the persistence of viable variola major virus in scabs maintained at various temperatures and relative humidities through 16 weeks of the hot season in Bangladesh (late May to mid-July). Her results are summarized in Table 2.11. The initial titre was $10^{8.3}$ plaque-forming units. Infectivity fell off rapidly at 35 °C, but at 4 °C viable virus was still present after 16 weeks, both at a relative humidity of 60–62% and in a desiccator (relative humidity, $<10\%$). At ambient temperature the relative humidity affected survival, virus persisting in a viable state for 8 weeks at high humidity and for 12 weeks at low humidity. These results confirm the observation of MacCallum & McDonald (1957) that virus viability was adversely affected by both high

Table 2.11. Viability of variola virus in scabs held at various temperatures and relative humidities for up to 16 weeks[a,b]

Week	At 35 °C 65–68% relative humidity	At 25.8–26.4 °C	
		85–90% relative humidity	< 10% relative humidity [c]
1	+	+	+
2	+	+	+
3	+	+	+
4	–	+	+
5	–	+	+
6	–	+	+
7		+	+
8		+	+
9		–	+
10		–	+
11		–	+
12			+
13			–
14			–

[a] Based on Huq (1976).
[b] + = virus demonstrable by CA membrane inoculation.
[c] In a desiccator, assumed to be < 10%.

temperatures and high relative humidity. Since these conditions prevailed in most of the countries in which endemic smallpox still occurred in the 1970s, prolonged survival of viable virus did not seem to pose a major long-term threat. However, virus could remain viable for long enough for fomites to present at least a short-term problem, especially in temperate climates.

The foregoing discussion relates mainly to the persistence of the viability of variola virus in scabs in relation to the threat that this might have posed to the eradication programme. One advantage of the heat resistance of variola virus was that it made possible the shipment of swabs and scabs from endemic countries to the WHO collaborating centres in Moscow and Atlanta, in which diagnostic laboratory studies could be carried out. Vesicle fluid or scab material was mailed in special containers, and although such transmission often took 2 weeks or longer, electron microscopy almost always revealed positive results in cases of smallpox, and chick embryo inoculation was often successful.

An epidemiologically important aspect of the resistance of variola virus to environmental conditions, discussed at greater length in Chapter 4, was its viability in droplets and droplet nuclei under various conditions of temperature and humidity. Short-term (60-minute) experiments showed that variola virus was relatively resistant in aerosols, and viability was only slightly less persistent at high relative humidities (Mayhew & Hahon, 1970). In other experiments, using vaccinia virus as a model, Harper (1961) found that over a longer time interval, viability in aerosols was greatest at low temperatures (10.5–11.5 °C) and low relative humidity (< 50%). The adverse effect of high relative humidity was greater at higher temperatures (Table 2.12). If, as is likely, this property also applies to variola virus, it has implications in relation to contact infection and the seasonal fluctuations in the incidence of smallpox, which was more common in the colder and drier months of the year (see Chapter 4).

SPECULATIONS ABOUT THE ORIGINS OF VARIOLA VIRUS

The elucidation of the history of smallpox over the last 2000 years, which is attempted in Chapter 5, involves much speculation, and alternative interpretations are possible for most of the ancient "plagues" that have been accepted by some authorities as outbreaks of

Table 2.12. The viability of vaccinia virus in aerosols at various intervals after spraying[a]

Temperature (°C)	Relative humidity (%)	Number of tests	Percentage viable at given times[b]						
			Seconds	5 minutes	30 minutes	1 hour	4 hours	6 hours	23 hours
10.5–11.5	20	1	94	68	78	82	79	81	66
	50	1	94	90	90	83	92	77	59
	82–84	2	97	81	71	79	59	60	27
21.0–23.0	18–19	2	97	86	80	66	46	45	15
	48–51	3	93	82	83	86	57	50	12
	82–84	3	112	96	73	66	24	18	Trace
31.5–33.5	17–19	2	80	67	67	61	51	33	13
	50	2	74	76	68	51	26	15	Trace
	80–83	2	88	88	54	36	5.9	1.2	Trace

[a] From Harper (1961).
[b] Initial titre $10^{7.7}$ plaque-forming units per millilitre of McIlvaine's buffer containing 1% dialysed horse serum.

smallpox. Suggestions as to how smallpox arose as a disease of humans are even more a matter of guesswork.

The Diversity and Specificity of Viruses of Man

There are some 20 well-characterized families of viruses of vertebrates, 18 of which contain one or more viral species that can infect man (White & Fenner, 1986). No less than 13 of these families include species which can be maintained in man as the sole vertebrate host; many of these viruses are specific for man and do not cause natural self-perpetuating infections in other vertebrates. On the other hand, each of these 13 families contains species of viruses that cause natural infections in vertebrates other than man. Among the family Poxviridae, 8 viral species, belonging to 4 different genera, can cause infections of man, but only 2 species—variola virus and molluscum contagiosum virus—are specifically human pathogens. For every specifically human virus the question of origins relates to how long ago, in the course of biological evolution, did the viral species in question exhibit the capacity to be maintained indefinitely by human-to-human (or proto-human-to-protohuman) spread.

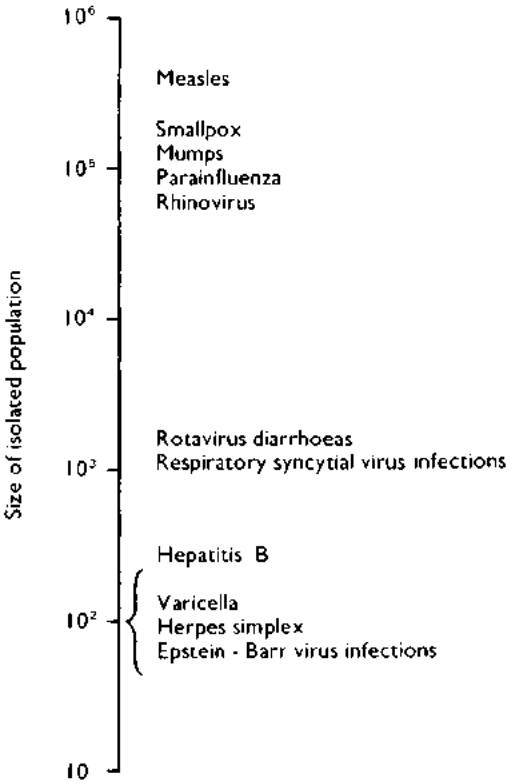


Fig. 2.11. Approximate sizes of populations required for maintaining the endemicity of several specifically human viral diseases. (From Black, 1982.)

Requirements for Human-to-Human Transmission

General principles

Whether or not a virus can be maintained indefinitely by passage from person to person in populations of various sizes depends on: (1) certain characteristics of the virus, notably its capacity to undergo antigenic change; (2) characteristics of the pathogenesis of the infection, especially the quality of the immune response and whether persistent infection or recurrence of infectivity occur; and (3) characteristics of the population biology of the host, notably the rate of accession of new susceptible subjects (Fig. 2.11). Viruses such as the herpesviruses, which exhibit persistent infection and recurrent infectivity, can be maintained in very small populations, even though they provoke a long-lasting immune response and circulate in a population of long-lived animals. However, viruses such as variola virus, which do not undergo antigenic change sufficient to overcome the immunity of previously infected hosts and which do not cause persistent infection with recurrent infectivity, will survive only in populations sufficiently large or with a sufficiently rapid turnover rate to ensure that some susceptible individuals are always likely to be infected. In this connection the turnover rate is affected by mobility and contact between population groups.

The case of variola virus

It was possible to eradicate smallpox in the 20th century because it was a disease that could persist only by transmission from one susceptible human being to another. In the absence of an alternative animal host, and lacking the capacity to cause endogenous recurrent disease in an individual who had been infected, the virus could persist in a population only if enough susceptible humans were constantly available to maintain a continuous chain of infection. Studies of the closely analogous situation in measles, both in the cities of the British Isles and the USA

(Bartlett, 1957, 1960) and in the islands of the Pacific (Black, 1966), suggest that a population of not less than 300 000–500 000 is necessary to sustain endemic measles. If, in the case of smallpox we reduce this to perhaps 200 000 because it spread less rapidly than measles, the disease could be sustained indefinitely in man as the sole host only after the introduction of irrigated agriculture—some 10 000 years ago—had initiated the first great population explosion.

What then could have been the source of the virus that caused the disease that has been recognized as smallpox for 2000–3000 years? Two possibilities exist: either man acquired the virus from some animal host in which it could be maintained because the animal occurred in larger numbers and had a much shorter generation time than had man, the hunter-gatherer; or else humans (or perhaps protohumans) had long been the host of an ancestral "variola virus" which produced a different sort of disease, one that could persist in small groups of hunter-gatherers, and subsequently changed its behaviour in the human host. We shall now examine these possibilities.

Possible Derivation of Variola Virus from another *Orthopoxvirus*

Variola virus is usually thought to have been derived from a closely related virus of some other animal, possibly an animal that was domesticated early and thus maintained close relations with early man. There are 4 orthopoxviruses known today that infect animals with which ancient man was or may have been in contact: camelpox, cowpox, ectromelia and monkeypox viruses.

Camelpox virus

Camelids evolved in the Americas and spread to Asia and North Africa some 3 million years ago. They would certainly have been hunted by early man, but were probably domesticated after sheep and cattle, perhaps some 5000 years ago. As it now occurs, camelpox virus is highly host-specific; its genome map is distinctive and quite different from that of variola virus.

Cowpox virus

This virus can infect a variety of different species of animal. It is probably maintained in nature in rodents, but occasionally infects man, cattle, cats and other domestic animals. Its genome is the largest of all the orthopoxviruses but deletion mutations occur commonly, producing progeny with smaller genomes. None of the strains of cowpox virus that have been examined has a genome that looks at all like that of variola virus.

Ectromelia virus

Now known only as the cause of mousepox in laboratory mice, ectromelia virus has a narrow host range and a distinctive genome map. Its original natural host was probably some field rodent.

Monkeypox virus

Since human monkeypox is clinically so like smallpox (see Chapter 29), it is natural to think of it as a possible progenitor of smallpox; or perhaps it would be more correct to think of a "proto-monkeypox" virus as having given rise to a "proto-variola" virus. The molecular biology of such a transformation is discussed in Chapter 30; suffice it to say that the DNA of monkeypox virus is no more similar to that of variola virus than is any other known orthopoxvirus DNA (see Fig. 2.7, 2.9 and 2.10).

At the present time monkeypox virus appears to occur naturally only in the tropical rain forests of central and western Africa. There is no evidence that human populations large enough to support the evolution and persistence of a virus with the characteristics of variola virus ever occurred in this part of the world in prehistoric times; 4000–5000 years ago populations of that size appear to have occurred only in the great river valleys of Egypt, the Fertile Crescent, the Indian subcontinent and eastern Asia. A disease recognizable as smallpox was present in Egypt in 1157 BC (if Ramses V did indeed die of smallpox) and in India and China perhaps as long as 2000 years ago. How could monkeypox virus, in its original form or as an evolving variola virus, move from western or central Africa to the Nile valley? The Sahara, as we now know it, would appear to have constituted an impossible barrier. But that was not always the case. Palaeoclimatic studies of Africa are in their infancy, but there is good evidence that the Sahara and the Sahel were much less arid in the period 9000 BC to 2000 BC than they are now, and supported popula-

tions of elephants and giraffes as well as ancient man (McIntosh & McIntosh, 1981). Further south, this savanna-like country merged into tropical rain forests that supported a rich fauna then, as they do now. In this kind of climatic regime, it is not impossible to conceive of the movement of newly evolving variola virus from areas far to the south and west into the Nile valley, where it might have persisted in the large human population of the Middle Kingdom.

Variola Virus as the Descendant of an *Orthopoxvirus* of Early Man

The other possibility is that variola virus had long existed among protohuman primates and our early ancestors. To explain its persistence in such small populations and the later emergence of smallpox as we know it, it is necessary to invoke the concepts of "*K*-selection" and "*r*-selection" (*K* refers to the carrying capacity of the environment; *r* to the maximal intrinsic rate of natural increase) used by ecologists to help to understand physiological and evolutionary adaptations, especially of insects and plants (Pianka, 1970; Southwood et al., 1974).

The human population was in a stage of *K*-selection until irrigated agriculture, which was developed some 10 000 years ago in the river valleys of Asia and northern Africa, vastly increased the potential human food supply and thus initiated the human population explosion that continues to this day—a situation in which *r*-selection became dominant. This change was accompanied by new evolutionary opportunities for viruses. During the phase of *K*-selection of their host, microbial parasites, including viruses, were also subject to *K*-selection. Only agents associated with prolonged or recurrent infectivity—for example, the human herpesviruses—could survive without recourse to an animal host. However, when the population became much larger and the annual input of susceptible individuals increased, viruses which produced diseases that were infectious for a brief period only, and that rendered the host immune thereafter, could survive and evolve. Under such conditions the viruses would be subjected to strong *r*-selection.

It is not difficult to accept this overall concept as being relevant to the evolution of the common respiratory and enteric viruses of man. It could be applied to smallpox in the following way: Man, the hunter-gatherer, and his forebears were hosts of a specifically human (or protohuman) "proto-variola" virus, which was able to persist in their small populations because infected individuals remained infectious for a long time. When irrigated agriculture allowed man to escape from the restrictions of *K*-selection, new opportunities existed for specifically human viruses, since susceptible populations were then large enough to support viruses that caused diseases which were infectious for a short period and rendered the host immune to reinfection. If a mutant arose from the "proto-variola" virus that multiplied much more prolifically (*r*-selection) and caused an acute generalized infection, it would soon replace its progenitor "proto-variola" virus wherever the human population was large enough. The result might be variola virus and smallpox. This hypothesis would have received strong support if the hypothetical "proto-variola" virus had been found among any of the hunter-gatherer populations in areas in which the population was until recent times subject to *K*-selection—the Americas, Australia and southern Africa. The behaviour of smallpox on first contact with these populations indicates that no such "proto-variola" virus existed there and this hypothesis remains unproved and unlikely.

Conclusions

We have to conclude that at present we do not know how, when or where variola virus originated. An origin from an orthopoxvirus of some other animal seems probable—and perhaps monkeypox virus may be suggested as the most likely candidate, on the grounds that it causes a disease in humans that is very like smallpox, rather than because of a particularly close resemblance between the DNAs of the respective viruses. Smallpox appears to have occurred for some 3000 years as a disease with the same characteristics as it exhibited up to the time of its eradication in 1977. The ultimate answer to its origin could come from studies of the nature and variability of the genomes of variola virus and other orthopoxviruses. However, with the eradication of smallpox, research on variola DNA is unlikely to be extensively pursued. Even if the problem is in principle soluble, we may never arrive at an answer.

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CHAPTER 3

THE PATHOGENESIS, PATHOLOGY AND IMMUNOLOGY OF SMALLPOX AND VACCINIA

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INTRODUCTION

The term pathogenesis is used to describe the mechanisms involved in the production of disease, including the spread of virus through the body and the physiological responses of the host organism to the infection, of which the most important is the immune response. The pathogenesis of smallpox could be studied in three ways: (1) by using material from human patients, which had the advantage of direct relevance but the disadvantage that planned experiments were not possible; (2) by conducting experiments with variola virus infections of non-human primates; and (3) by conducting experiments with "model" infections—ectromelia (mousepox) in mice, vaccinia (rabbitpox strain) in rabbits, and monkeypox in monkeys. Each of these approaches had advantages and disadvantages. With human subjects, investigation during life was limited to the sampling of body fluids, skin biopsy (rarely), and the examination of postmortem material. No investigations were possible during the incubation period, when most of the critical events in the spread of the virus through the body and the initiation of the immune response occurred. Monkeys that developed a rash after infection with variola virus by the respiratory route probably provided the best model system, but monkeys are expensive animals and such experiments could only be undertaken in microbiologically highly secure laboratories. For want of a better alternative, therefore, most investigations that are relevant to an understanding of the pathogenesis of smallpox have been carried out with other orthopoxviruses, especially mousepox virus, since so much is known of the genetics and immune response in mice. But mice are not men and mousepox is not smallpox. Arguments by analogy must therefore be developed cautiously. The results of these diverse investigations will be summarized in this chapter, and the information collated to provide an integrated picture of the pathogenesis and immunology of smallpox.

Following the analysis of the pathogenesis of smallpox, we proceed to a description of the pathology and histopathology of smallpox and vaccinia, which have been studied with material from autopsies on fatal cases and, in a few cases, by taking biopsies from skin lesions. Most of this work was carried out early in this century; the most recent and most comprehensive descriptions of the pathology and histopathology of smallpox were published by Bras (1952a,b).

Finally, this chapter presents an account of the immune responses in smallpox and vaccinia, which provides the rationale of the use of the tool that made the eradication of

smallpox possible—Jennerian vaccination. Immunological intervention designed to prevent human diseases began in the 10th century, with variolation, and entered a new "scientific" phase when vaccination against smallpox was introduced in 1798 (see Chapter 6). Over the past three-quarters of a century an enormous literature has accumulated describing the mechanisms by which vaccination induced immunity to smallpox. Unfortunately, because methods of studying cellular aspects of immunity were developed relatively recently, most of these investigations were concerned only with humoral immunity. In spite of its long history, the immunology of both smallpox and vaccination against it are still imperfectly understood.

THE PORTAL OF ENTRY OF VARIOLA VIRUS

Infection with variola virus occurred via the respiratory tract, by inoculation through the skin, or, rarely, via the conjunctiva or the placenta.

The Respiratory Tract

Epidemiological evidence indicates that the usual mode of entry of variola virus was via the respiratory tract and that excretions from the mouth and nose, rather than scab material, were the most important source of infectious virus. In theory, infection by inhaled virus could have occurred via the mucous membranes of the mouth, the nasal cavity, or the oro- or nasopharynx; or via the alveoli of the lungs. However, careful study of these sites in fatal cases of smallpox failed to disclose any evidence of a "primary lesion" there. Nor were patients infectious before the enanthem appeared, at the end of the incubation period. It seems, therefore, that the primary infection in the mouth, pharynx or respiratory tract did not produce a sizeable lesion nor did the lesion of infection ulcerate and release virions on to the surface.

In the absence of data from human smallpox it is pertinent to look at an animal model. Observations by Roberts (1962a) on mousepox suggest a possible sequence of events. Fluorescent-antibody staining of sections taken after exposure of mice to aerosol infection showed that the first cells to be infected were mucosal cells of the upper and lower respiratory tract and alveolar macrophages. Virus did not spread beyond the respiratory tract until the 3rd day after infection, when it was found in free macrophages in the draining lymph nodes. At no stage did a substantial "primary lesion" develop in the respiratory tract, like that found, in both mousepox and smallpox, after infection by cutaneous inoculation.

Inoculation Smallpox

The clinical picture of inoculation smallpox, which sometimes occurred accidentally but was usually due to variolation by the cutaneous route, is described in Chapters 1 and 6 (see Plates 6.1–6.3). A local skin lesion appeared by the 3rd or 4th day. Fever and constitutional symptoms began on the 8th day, and the rash, which was usually much less severe after variolation than in naturally acquired smallpox, appeared on the 10th or 11th day. Thus the incubation period appeared to be 2–3 days shorter than in "natural" smallpox (see Chapter 1, Fig. 1.3). Observations on mice infected with mousepox by scarification (Roberts, 1962b) suggest that the shorter incubation period may have been due to the fact that after dermal infection infected macrophages were transported to the local lymph nodes and thus to the circulation within the first 24 hours, whereas after respiratory infection viral dissemination by macrophages was delayed until the 3rd day. Viraemia and rash would therefore occur a few days earlier after dermal infection.

The Conjunctiva

If infection via the conjunctiva occurred at all in smallpox, it was very rare (Rao, 1972). However, Kempe et al. (1969) noted that occasionally variolous conjunctivitis, confirmed by viral isolation, occurred at or even before the onset of the pre-eruptive fever. In no case was the interval between conjunctivitis and rash as long as that found between the appearance of the primary lesion and the rash in inoculation smallpox, which makes it difficult to decide whether the conjunctiva was actually the portal of entry.

Congenital Infection

Variola major was always severe in pregnant women (see Chapter 1). In Rao's (1972) series, abortions or stillbirths occurred in

35% of those in whom pregnancy terminated and observations were possible. The majority (55%) of 113 babies born in hospital died within 15 days, usually within 3 days. Congenital smallpox was recognized in only 10 of these, but some children may have died before a rash appeared. Nevertheless, at least half of the babies did not acquire infection *in utero*.

Being so much milder than variola major, cases of variola minor in pregnant women provided better data on congenital infections. There were 150 pregnant women in Marsden's (1936) series of 13 686 cases of variola minor. Only 6 abortions are known to have occurred, but Marsden thought that smallpox sometimes played a part in the induction of labour during the last 2 months of pregnancy. Sixteen women were confined in the smallpox hospital and bore 16 live infants (including 1 pair of twins) and 1 stillborn fetus with a papulo-vesicular eruption. Twenty-seven women were delivered of live infants just before admission to hospital, labour having begun at the time of the pre-eruptive fever. Marsden & Greenfield (1934) reported an analysis of 34 of the cases concerned. In 17 cases the baby escaped *in utero* infection. In 2 of these babies, born during the mother's convalescence, the vaccination did not take; the rest were successfully vaccinated, but 4 of them later contracted smallpox. Only 2 of the 17 babies who contracted variola minor *in utero* died. The course of the disease was never coincident in mother and baby; symptoms in the baby usually occurred 9–11 days after those in the mother, an interval similar to the incubation period of inoculation smallpox. The fetus was presumably infected by the growth of virus in the placenta, which would have been infected during the stage of secondary viraemia (see below).

Observation of a laboratory model (pregnant mice infected with an attenuated strain of mousepox virus) revealed that the placentas were infected and the virus grew extensively in the fetuses (Mims, 1969). Some live births occurred, but all such mice had widespread lesions which proved lethal, although the mothers had suffered only a mild disease.

THE SPREAD OF INFECTION THROUGH THE BODY

The only sources of virus accessible for study in human smallpox during the incubation period were various secretions of contacts of cases, some of whom ultimately got smallpox, so that in order to study the spread of infection through the host it was necessary to use animal models. Four such models have been studied: mousepox in mice, rabbitpox in rabbits, and monkeypox and smallpox in monkeys and apes.

Mousepox

The pioneering work on the pathogenesis of generalized orthopoxvirus infections, which provided a model that proved useful in understanding the pathogenesis of chickenpox (Grose, 1981) as well as that of smallpox, was carried out with mousepox (Fenner, 1948a,b). Mice that did not die from acute viral hepatitis developed a generalized pustular rash (Fenner, 1948c) and the symptoms of the naturally occurring disease could be reproduced by the footpad inoculation of mice with a small dose of virus.

The course of events after footpad inoculation was followed by sacrificing mice at frequent intervals and titrating the viral content of certain organs—the inoculated foot, the regional lymph node, the spleen, the skin, and the blood. The results indicated that the sequence of events during the incubation period in mousepox followed a consistent pattern (Fig. 3.1). If the appearance of the primary lesion was taken as the end of the incubation period, it was evident that this symptom-free period was occupied by a complex series of events in which the virus passed in a stepwise fashion through the body: infection, replication, and liberation—usually accompanied by cell necrosis—first at the site of inoculation, then in the regional lymph node, and then in the deeper lymph nodes or perhaps directly into the bloodstream. It seems from the work of Mims (1964), who used fluorescent-antibody staining to identify virus-infected cells, that in the liver and spleen the phagocytic cells were the first infected. When infection had breached the macrophage barrier the virus replicated very extensively in the parenchymal cells of the liver and in the spleen, both of which usually showed semiconfluent necrosis. A day or so after infection of the spleen and liver, large amounts of virus were liberated into the bloodstream, and during this secondary viraemia focal infection of the skin, kidneys, lungs, intestines and other organs occurred. There was again an interval during which the virus replicated to reach a high titre before visible

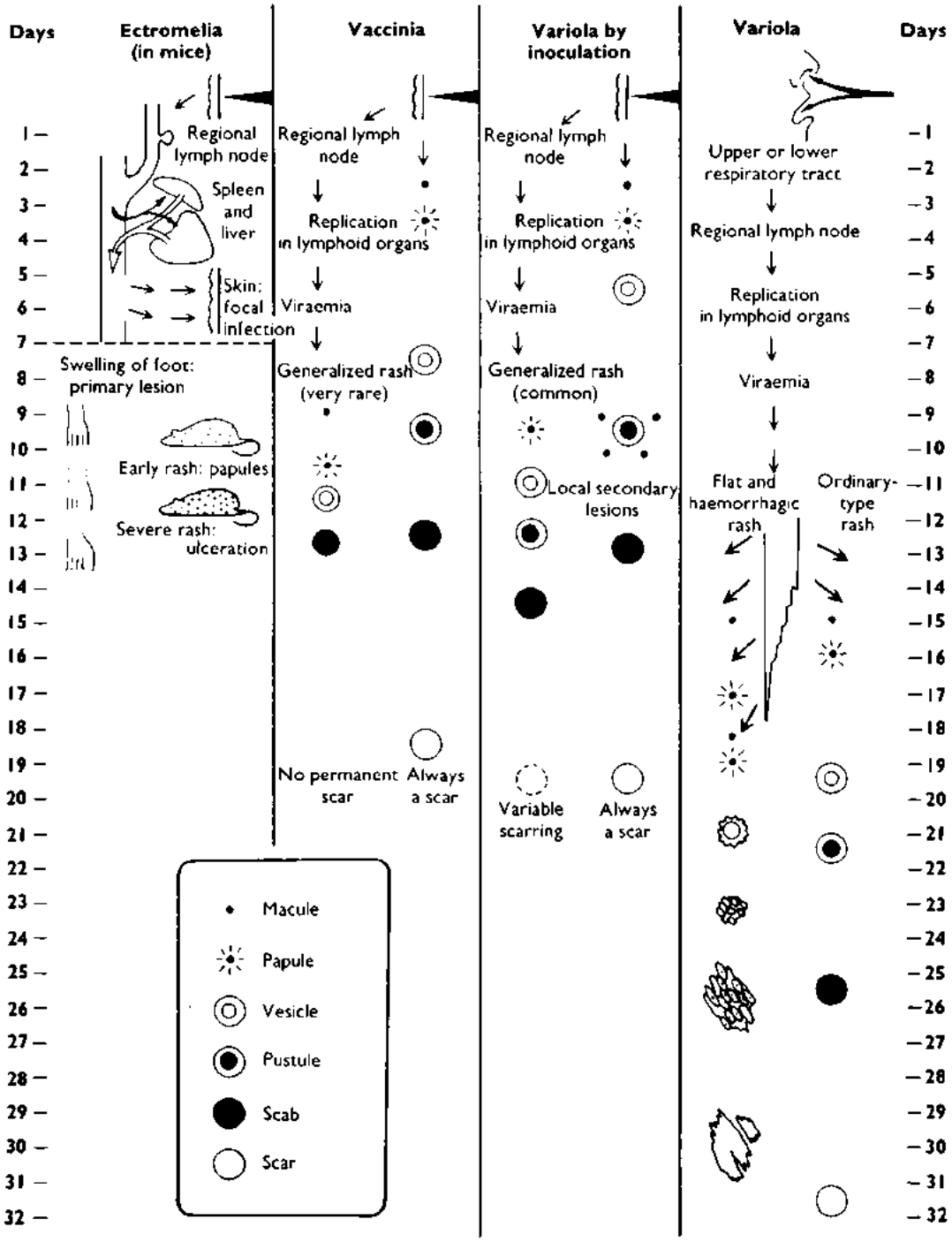


Fig. 3.1. The spread of virus around the body and the evolution and healing of skin lesions in a model system (ectromelia, after Fenner, 1948b), and in vaccinia, inoculation smallpox, and "natural" smallpox in man. For vaccinia and inoculation smallpox, the right-hand column represents lesion at site of inoculation, left-hand column represents generalized skin lesions. (Based on Dixon, 1962.)

changes were produced, so that a period of about 2 or 3 days usually elapsed between the appearance of the primary lesion and the focal lesions of the secondary rash (Fig. 3.1). The secondary viraemia was mainly cell-associated and only small amounts of virus could be recovered from plasma or serum. Mims (1964) demonstrated by fluorescent-antibody staining that circulating lymphocytes and monocytes contained viral antigen.

Although this work provided a general explanation of what happened during the long incubation period of the generalized exanthemata (Fenner, 1948b), mousepox is not a satisfactory model for smallpox. Apart from the difficulty of comparing events in mice and men, the usual mode of infection in mousepox is via skin abrasions (it is thus analogous to inoculation smallpox), rather than by the oropharynx or respiratory tract. More important, mousepox appears to be unusual among the generalized orthopoxvirus infections, and certainly different from human smallpox, in that the spleen and liver are major target organs for viral replication. In mousepox these organs are clearly the "central foci", established during the incubation period, from which virus is continually released into the bloodstream, with ensuing infection of the skin and other organs and tissues.

Subsequent research into the pathogenesis of smallpox was carried out with other laboratory models—rabbitpox and monkeypox in rabbits and monkeys respectively, and non-human primates experimentally infected with variola virus.

c. 1960

Plate 3.1. Frank Fenner (b. 1914). Formerly Professor of Microbiology in the John Curtin School of Medical Research of the Australian National University, Canberra. He is shown here inoculating eggs on the chorioallantoic membrane, a method used for assays of orthopoxviruses and neutralizing antibodies to them, and for the differentiation of variola virus from other poxviruses.

Rabbitpox

Studies on the pathogenesis of rabbitpox, a severe disease of rabbits produced by certain strains of vaccinia virus, did not add much to the picture that had emerged from experiments with mousepox. After rabbits were infected by the respiratory route (Bedson & Duckworth, 1963; Westwood et al., 1966), virus spread through the body in a stepwise manner. Viral isolations could always be made from the lungs, and very high titres occurred in the gonads and the adrenal glands. The incubation period, from infection until the onset of fever, was 4–6 days. A rash usually appeared on about the 6th day, although often rabbits died before the rash became evident ("pockless" rabbitpox; Christensen et al., 1967).

In spite of the early replication of rabbitpox virus in the lung, rabbits were not infectious until nasal and conjunctival discharges appeared, and environmental contamination appeared to be maximal 6–7 days after infection. Examination by fluorescent-antibody staining revealed that after aerosol infection primary lesions developed at two distinct sites in the respiratory tract—the bronchioles and the alveoli. It was also found that as well as being spread to the bloodstream via the lymphatics, rabbitpox virus could spread directly from the bronchiolar or alveolar lesions to adjacent blood vessels.

Viraemia was mainly leukocyte-associated. Animals that died early, before the rash appeared, had viraemias which increased exponentially to reach very high titres at the time of death; those that died later had much lower titres (Westwood et al., 1966). This situation invites comparison with the levels of viraemia in haemorrhagic-type and discrete ordinary-type smallpox respectively (see below).

Monkeypox

Cynomolgus monkeys are highly susceptible to monkeypox and usually develop a

generalized rash (Magnus et al., 1959). Wenner and his colleagues (review: Cho & Wenner, 1973) studied the pathogenesis of monkeypox in cynomolgus monkeys infected by intramuscular inoculation. These investigations confirmed that in orthopoxvirus infections of primates, as well as in those of mice and rabbits, there was a stepwise progression of infection, a generalized rash developing after viraemia had been established owing to the replication of virus in the internal organs. Prior to the development of the rash the virus replicated in the spleen, tonsils and lymph nodes, without producing extensive or severe lesions. Generalized lymphadenopathy developed in the 1st week after infection and persisted until the end of the 3rd week. Enlargement of the cervical and inguinal lymph nodes is a feature of monkeypox infections in chimpanzees (McConnell et al., 1968) and humans (see Chapter 29).

Variola Virus Infection in Non-human Primates

The monkey was the first animal to which variola virus was transmitted (Zuelzer, 1874) and monkeys were extensively used in early studies of cross-immunity between variola and vaccinia (Brinckerhoff & Tyzzer, 1906; Horgan & Haseeb, 1939). Experimental studies of the pathogenesis of smallpox in the cynomolgus monkey (*Macaca irus*) were carried out by Hahon & Wilson (1960) and Noble & Rich (1969). After an incubation period of about 6 days, inoculated animals usually developed a generalized rash that was sparse on the face, hands and feet—sites where the rash was usually more intense in human smallpox. After infection by aerosol, variola virus replicated in the lung, and secondary sites of replication were established in the lymph nodes before viraemia occurred. Although the study was complicated by pre-existing bronchopneumonia, Hahon & Wilson (1960) failed to demonstrate any major focus of local viral replication in the lungs even though they yielded a substantial amount of virus during the incubation period. Natural transmission to other monkeys could occur by the airborne route, with an incubation period of 8–16 days (see Chapter 30, Fig. 30.1).

Only 2 out of 109 rhesus monkeys (*Macaca mulatta*) infected by aerosol with variola major virus died, but all developed fever on the 5th day and a rash between the 6th and 11th days (usually on the 7th or 8th day). Assay of various organs revealed high titres in the lungs and skin, with occasional isolations from the blood and spleen. Large amounts of virus were recovered from all organs tested in a monkey that died on the 11th day.

Rao et al. (1968b) showed that cortisone greatly increased the severity of smallpox in bonnet monkeys (*Macaca radiata*) inoculated intradermally with variola virus. None of 14 controls died, whereas 12 of the 16 animals given cortisone and 1 pregnant monkey died after suffering from a much more severe primary lesion and generalized rash than were seen in the control animals. Virus could be readily recovered from most of the internal organs of the cortisone-treated animals at the time of their death. This increased severity is comparable to that seen in pregnant women who contracted variola major (Chapter 1).

Orang-utans (Gispen, 1949) and chimpanzees (Kalter et al., 1979) can be naturally infected with variola virus (see Chapter 30), and may suffer a severe disease with an extensive rash (see Plate 30.1). Baboons (*Papio cynocephalus*) inoculated with variola virus by scarification developed a rather "dry" local lesion but no rash; virus was recovered from the blood, throat swabs and rectal swabs between the 4th and the 7th days after infection (Heberling et al., 1976).

Smallpox in Human Subjects

The 4th and 5th columns of Fig. 3.1 illustrate diagrammatically, on the basis of available data, the sequence of events in human smallpox after intradermal inoculation and after infection via the respiratory tract. Investigations in human subjects relevant to the pathogenesis of smallpox have been limited to virological and serological tests carried out in hospitalized patients or case contacts. Such studies were limited to the examination of blood, urine, and throat washings in cases after the onset of fever and throat washings from case contacts during what was potentially the incubation period. These investigations were important because they provided information that permitted arguments about the pathogenesis based on model systems to be developed with more confidence.

Viraemia

No precise observations have been made on the distribution of variola virions among the various components of the blood in cases of smallpox; by analogy with other poxvirus infections viraemia would have been expected to be primarily cell-associated. Most assays of viraemia in smallpox were made with serum or lysed whole blood, the material being assayed on the chorioallantoic membrane of chick embryos (Downie et al., 1950, 1953, 1969b; Mitra et al., 1966).

Although viraemia must always have occurred, virus was only rarely recovered from the blood or serum from cases of ordinary-type smallpox. Downie et al. (1950, 1953) and Mitra et al. (1966) recorded one or two positive results out of many attempts in such cases and then only in the first few days of the disease. The picture in haemorrhagic-type smallpox was quite different. Virus was readily recovered from the blood of all cases and the titres were usually high, as determined by confluent lesions on the membrane (Downie et al., 1953, 1969b) or by titration (Mitra et al., 1966; Sarkar et al., 1969). In these patients viraemia usually persisted until the patient died. Downie et al. (1969b) noted that viraemia was consistently much higher in cases of early than of late haemorrhagic-type smallpox. They also examined the serum by gel-precipitation and complement-fixation tests for the presence of soluble antigens of variola virus; cases of haemorrhagic-type smallpox usually had an antigenaemia (Fig. 3.2). Complement-fixation tests revealed antigenaemia in 31 out of 46 sera tested, the level being, in general, proportional to the extent of the viraemia. The gel-precipitation test was less sensitive, revealing antigen in only 16 out of 45 sera tested, all from cases of early haemorrhagic-type smallpox with severe viraemia.

Thus haemorrhagic-type smallpox appears to have been associated with overwhelming infection and the continued release of virus into the bloodstream; in ordinary-type smallpox demonstrable viraemia was usually restricted to the pre-eruptive and early eruptive stages of the disease.

Oral and pharyngeal secretions

Because there is no tough stratum corneum on the oral and pharyngeal mucosae, the lesions of the enanthem ulcerated very soon after their formation (see Plate 3.7), releasing

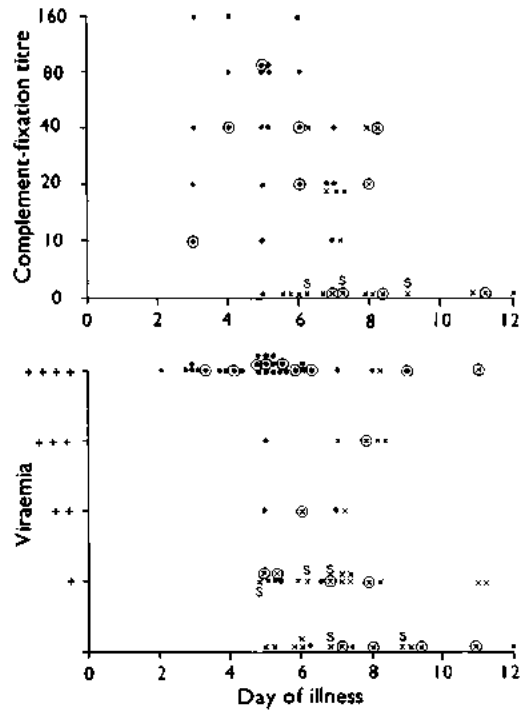


Fig. 3.2. Antigenaemia and viraemia in haemorrhagic-type smallpox. • = early haemorrhagic type; × = late haemorrhagic type; ◉, ⊗ = vaccinated; S = survived (all other cases died). (From Downie et al., 1969b.).

large amounts of highly infectious virus into the saliva. The viral titres in throat swabs were at their maximum on the 3rd and 4th days of the disease (i.e., at the onset of the rash) and were highest, and persisted for the longest period, in the most severe cases (Sarkar et al., 1973a; see Chapter 4). In fatal cases virus was usually still present in the throat swabs at the time of death; in non-fatal cases it was found for 7–9 days after the onset of fever in discrete ordinary-type smallpox and sometimes for as long as 13 days in non-fatal confluent ordinary-type smallpox.

More important, from the point of view of pathogenesis, are reports of the recovery of virus in throat washings taken from case contacts who developed smallpox. Careful laboratory studies by Sarkar and his colleagues showed that household contacts of cases of smallpox sometimes harboured detectable amounts of variola virus in their throats. Using a single throat swab, Sarkar et al. (1973b) isolated variola virus in 34 out of 328 subjects who had been in close household contact with 52 index cases of smallpox for periods of between 4 and 8 days. Only 4 of the

34 contacts with positive throat swabs subsequently developed smallpox, the symptoms appearing 5–6 days after virus was isolated. In a follow-up study (Sarkar et al., 1974), positive results were reported in 5 out of 51 close family contacts examined, only 1 of whom subsequently developed smallpox (Table 3.1). Serial testing showed that virus could sometimes be recovered from the throats of vaccinated contacts, most of whom did not develop clinical smallpox, for as long as 10 days.

F. Huq (personal communication, 1982) confirmed Sarkar's findings, but recorded a much smaller proportion of positive results. Using a similar laboratory procedure, she found 3 positives (all in unvaccinated subjects, and all of whom subsequently developed smallpox) among 168 contacts who were examined within a week of the development of rash in the index subjects.

The finding of virus in throat swabs of contacts of acute cases is not altogether surprising; presumably virus replicating in an asymptomatic "primary lesion" in the fauces or elsewhere in the oropharynx was released into the oral secretions or could be obtained by swabbing the fauces. However, such virus as was present in the oral secretions during the incubation period was of little or no epidemiological importance. The onset of infectivity in the vast majority of cases coincided with the development of the rash and was due to the release of virus from the ulcerated surfaces of the lesions of the enanthem.

The Dissemination of Virus through the Body

Orthopoxvirions were principally disseminated through the body in the lymph and bloodstream as cell-associated particles, although some virus was always found free in plasma. In cell cultures, enveloped forms of vaccinia virus were more important than non-enveloped forms in the dissemination of virions over a distance (Boulter & Appleyard, 1973), as shown by the "anti-comet" test (see Plate 3.10). Payne (1980) showed that the capacity to spread to distant cells in monolayer cultures and to distant organs in the mouse was correlated with the production of enveloped virions (Table 3.2).

Unfortunately, no observations were ever made to determine whether enveloped virions occurred in infections of monkeys or human beings with variola virus, nor have such observations been reported with ectromelia or monkeypox viruses.

THE RASH

The primary event for the production of the focal lesions of the rash in orthopoxvirus infections is the localization, in the small blood-vessels of the dermis, of virus particles that circulate in the bloodstream, either freely in the plasma or more commonly within virus-infected leukocytes. Subsequently, adjacent epidermal cells are infected and the skin lesion develops as described below.

In the infection of laboratory animals with orthopoxviruses, skin areas so treated as to promote a local inflammatory response are associated with an increased density of skin lesions (vaccinia in rabbits: Camus, 1917; ectromelia in mice: Fenner, 1948a). Numerous observations (Ricketts, 1908; MacCallum & Moody, 1921) attest to the effect of mild trauma leading to local vasodilatation on the density of skin lesions in different parts of the

Table 3.1. Prolonged presence of variola virus in throat swabs from contacts of cases of smallpox (data expressed as log pock-forming units per swab)

Serial no. of contact	Age	Vaccination scar	Days after onset of fever in index case[a]									
			4	6	10	11	12	14	17	19	21	23
26[b]	55 years	+	..	4.0	..	2.0	Developed smallpox					
29[b]	5 months	–	3.0	..	..	2.0	Developed smallpox					
1[c]	23 years	+	..	..	..	..	1.9	1.9	1.8	1.7	1.5	0
2[c]	22 years	+	..	..	..	..	3.0	2.9	2.9	1.9	1.6	0
3[c]	24 years	+	..	..	..	..	..	3.3	2.9	2.0	2.0	0
4[c]	45 years	+	..	..	..	..	1.7	..	..	Developed smallpox		
5[c,d]	28 years	+	..	1.8	0	0	..	..	..	..	..	..

[a] .. = data not recorded.
[b] Sarkar et al. (1973b).
[c] Sarkar et al. (1974).
[d] A nurse, revaccinated almost every year, in close contact with a case of haemorrhagic-type smallpox.

The Significance of Enveloped Virions

Viruses belonging to 10 of the 17 viral families that cause disease in humans are enveloped—i.e., their outer surface is a lipoprotein envelope consisting of cellular lipids and virus-specific polypeptides. Destruction of the envelope, for example by lipid solvents, usually completely destroys infectivity. The orthopoxviruses are exceptional in that although virions released from cells are enveloped (see Chapter 2, Plate 2.9), absence of the envelope is associated with only a slight decrease in the infectivity/particle ratio. Although non-enveloped particles, whose surface consists of the outer membrane (see Chapter 2, Fig. 2.1), have almost the same infectivity as enveloped particles and spread effectively by cell-to-cell contact, they do not spread as well around the body as do enveloped virions (Table 3.2).

Because there are two kinds of infectious particle, two kinds of neutralizing antibody can be produced which neutralize enveloped and non-enveloped particles respectively. Both kinds of neutralizing antibody are produced during all orthopoxvirus infections. Antibody that neutralizes only enveloped particles can be produced by immunization with purified viral envelopes. Antibody that neutralizes only non-enveloped particles is produced by inoculation with suspensions of particles obtained by disrupting cells and then inactivated. Neutralizing antibody to non-enveloped virions provides much less effective passive protection against generalized orthopoxvirus infections than does antibody to enveloped virions (see Table 3.5). The two kinds of particle also produce different kinds of cell-mediated immunity, cytotoxic T cells being generated only during infections and not by suspensions of inactivated virions. For these reasons inactivated vaccines provide only partial immunity in experimental animals and have proved useless for vaccination against smallpox.

body in smallpox (the "garter" effect). Vasodilatation due to sun and wind may have played a part in the greater density of lesions on the face and the extensor surfaces of the hands and arms than elsewhere on the body, but this factor does not explain the highly characteristic "centrifugal" distribution of skin lesions in smallpox, for which no satisfactory physiological explanation has yet been provided.

TOXAEMIA

All clinical observers have commented on the "toxic" appearance of patients with variola major, especially those suffering from flat-type or haemorrhagic-type smallpox. Although very severe cases did occur—extremely rarely—in variola minor, there was usually a great contrast in the general appearance and condition of patients with variola major and variola minor with approximately the same numbers of pustules. The patient with acute variola major was usually very sick, whereas the patient with variola minor of apparently similar severity (in terms of the number of skin lesions) might well be ambulant.

No adequate explanation is available to elucidate either the toxaemia of variola major or the difference in severity between cases of variola major and variola minor with rashes of similar extent. Viral antigen was readily demonstrable in the plasma of patients with severe smallpox (Downie et al., 1953, 1969b; see Fig. 3.2). The formation of immune complexes between such antigens and IgM antibodies, and the associated activation of complement, might have initiated a series of physiological effects that produced the so-called "toxic" symptoms of variola major.

Seeking an explanation of the cause of death in smallpox, Boulter et al. (1961a) examined various physiological parameters in a model system—rabbitpox. The only consistent physiological changes observed in sick rabbits were extreme hypotension, leading to a shock-like syndrome, decreased urinary output and a rise in blood-urea and plasma-potassium levels. Death seemed to be due to lethal concentrations of potassium ion, which occurred possibly as a consequence of the severe hypotension. No information is avail-

Table 3.2. Relationship of *in vitro* virus release to *in vitro* and *in vivo* parameters of virus dissemination[a]

Vaccinia strain	RK 13 cells			Mouse virulence[b]	
	Virus production				
	Enveloped virions[c]	Ratio: Non-enveloped / Enveloped	Formation of "comets"[d]	Mortality (%)	Brain titre[e]
South Africa	5.6	250	-	0	—
Cape Town	5.7	100	-	0	—
Venezuela	6.0	160	-	0	—
Lister	6.3	300	-	0	—
Tashkent	6.6	160	-	0	—
WR	6.6	300	-	85	4.7
Lederle 7N	6.7	250	-	0	—
Hall Institute White	6.8	50	-	0	—
Dairen	7.0	16	-	0	2.7
Lafontaine	7.6	40	±	0	3.6
IHD-W	8.0	12	+	25	3.3
Gallardo	8.3	5	+	25	3.3
IHD-J	8.3	6	+	70	4.6

[a] Based on Payne (1980).
[b] After incubation with 10^6 plaque-forming units intranasally.
[c] Titre in $\log_{10}$ plaque-forming units per millilitre.
[d] In cell monolayers with liquid overlay (see Plate 3.10).
[e] Titre in $\log_{10}$ plaque-forming units per gram of brain.

able on blood-pressure or blood-potassium changes in severe cases of smallpox.

PATHOLOGICAL ANATOMY AND HISTOLOGY OF SMALLPOX

General Observations

As described in the appropriate chapters of this book, a wealth of information about the virology, epidemiology and control of smallpox has emerged from the work carried out since the inception of the Intensified Smallpox Eradication Programme in 1967. However, what Bras (1952a) pointed out more than 30 years ago was still true at the time of global eradication: in recent years smallpox usually occurred, on a large scale, in places where pathological studies were difficult. Prior to Bras's own important work one has to go back to Councilman et al. (1904) for a comprehensive description of the pathological anatomy and histology of smallpox. Some years later Lillie (1930) produced a review of published reports on the histopathology of smallpox and vaccinia. A useful description of the histology of the skin lesions in variola major was provided by Michelson & Ikeda (1927), while MacCallum & Moody (1921) and Jong (1956) obtained skin biopsies from patients suffering from variola minor.

In earlier studies interpretation of the pathological changes, particularly in the lungs, was complicated by the presence of secondary infection with streptococci and other organisms (see Councilman et al., 1904). More recent observations have shown that although bacterial infection did sometimes complicate smallpox, pustulation was viral and not bacterial in origin, and the high mortality of variola major was due to viral effects, not secondary bacterial infection. The case-fatality rate was not significantly reduced by the use of antibiotics. Bacterial complications were rare in the cases described by Bras (1952a), most of which were treated with antibiotics.

A striking feature of the pathology of smallpox is that although it was a generalized disease, often of great severity, specific pathological changes were in large part limited to the skin and mucous membranes, except for the widespread haemorrhages found in various organs in early haemorrhagic-type smallpox.

The Skin Lesions

In order to understand the histopathology of the skin lesions in smallpox it is necessary to appreciate the relationships between different parts of the skin, as illustrated in Fig. 3.3. The epidermis, where the pustule develops, contains no blood or lymphatic vessels and its tough outer layer, the stratum corneum, is impermeable to viruses. The dead

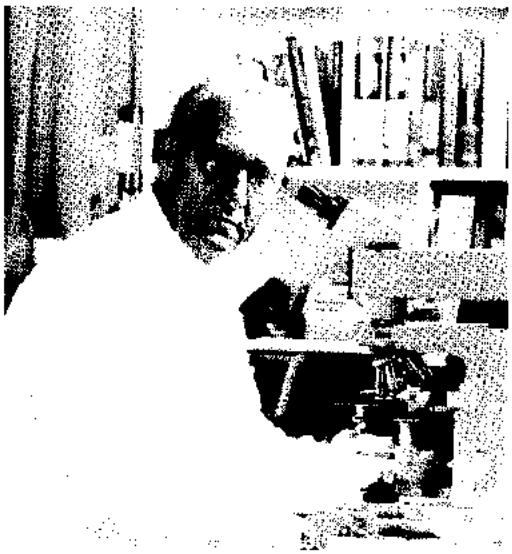


Plate 3.2. Gerrit Bras (b. 1913). Professor of Pathology at the National University in Utrecht, Netherlands. Bras carried out a classical study of the pathological changes in variola major during the epidemic in Java after the Second World War.

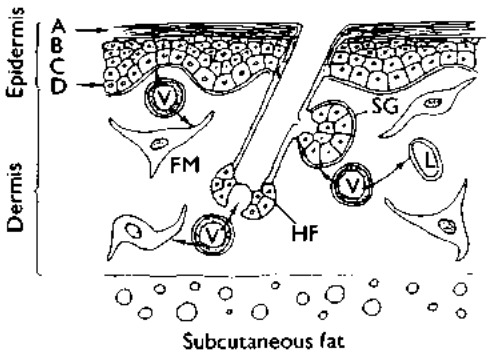


Fig. 3.3. The structures of importance in the pathogenesis of the skin lesions of smallpox. The epidermis consists of several layers of living cells, the stratum Malpighii, covered by a layer of dead keratinized cells, the stratum corneum (**A**). The basal layer of the stratum Malpighii consists of dividing cells, the stratum germinativum (**D**), above which there is a variable number of layers of cells, called the stratum spinosum (**C**), and just below the stratum corneum a layer of cells that contain keratohyalin granules, the stratum granulosum (**B**). The dermis contains blood vessels (**V**), lymphatic vessels (**L**) and fibroblasts and macrophages (**FM**). The ground substance contains collagenous, reticular, and elastic fibres. The hair follicle (**HF**) and sebaceous gland (**SG**) are appendages of the epidermis.

keratinized cells of the stratum corneum are continually being rubbed off and replaced from below, cell multiplication occurring in the stratum germinativum, which is separated from the dermis by a thin basement membrane. Of the three appendages of the skin—hair follicles, sweat glands and sebaceous glands—only the last are destroyed by variola virus, and then, to any extent, only by variola major virus.

The appearance of the skin lesions, their temporal development and their characteristic distribution are described and illustrated in Chapter 1. The following description of the histology of the skin lesions at various stages of the disease draws mainly on postmortem material from variola major described by Michelson & Ikeda (1927) and Bras (1952a,b) and biopsy material obtained from cases of variola minor (MacCallum & Moody, 1921; Jong, 1956).

Early changes in the dermis

Bras (1952a) noted that the histological picture in the skin lesions in all types of variola major, whether haemorrhagic or not, was essentially the same. The development and evolution of a skin lesion are shown in Plate 3.3. The earliest change was a dilatation of the capillaries in the papillary layer of the dermis, followed by swelling of the endothelial cells in the walls of these vessels, stasis of mononuclear cells within the lumen, and subsequently perivascular cuffing with lymphocytes, plasma cells, macrophages and occasionally eosinophilic granulocytes (Plate 3.3A). Biopsies from cases of variola minor (MacCallum & Moody, 1921) showed that the affected papillae were oedematous, with extravasation of erythrocytes and leukocytes, at a time when the overlying epidermis was unchanged or showed at most only an early vacuolation of the epidermal cells.

Epidermal changes

Following the early changes in the dermal vessels, lesions developed in the adjacent part of the epidermis, where all subsequent changes occurred. The cells of the stratum Malpighii became swollen and vacuolated and underwent what was described as "ballooning" degeneration. This occurred in a sharply demarcated area and only a small number of cells separated the centre of the lesions from the surrounding normal skin (Plate 3.3A and B). The degenerated cells were swollen, they stained faintly with acid dyes, and the characteristic B-type inclusion bodies (Guarnieri

bodies: see Chapter 2, Plate 2.7) could be found in the cytoplasm.

Early in the disease, in sections stained with haematoxylin and eosin, the inclusion bodies appeared as round or oval homogeneous faintly basophilic or acidophilic masses lying close to the nucleus. One or more were present in a cell and each was usually surrounded by an unstained halo. In older lesions the inclusions had a granular appearance and irregular outline and sometimes occupied a large part of the cytoplasm of infected cells. Intranuclear inclusions have also been described in cells infected with variola virus (Torres, 1936), but not with other orthopoxviruses. They were not a conspicuous feature of the lesions, but Downie (1965a) confirmed that they did sometimes occur. Their significance is unknown.

The cells continued to increase in size, the cytoplasm became fainter and the nucleus usually disappeared by lysis. Soon after this the cell membranes ruptured and the vacuoles coalesced to produce the early vesicle by what was called "reticulating" degeneration (Plate 3.3C). Because this coalescence occurred very quickly a true papule was rarely seen; almost from the beginning the lesion was already vesicular.

Vesiculation

The reticulating degeneration which produced the vesicle occurred exclusively in the middle and upper layers of the stratum spinosum; the basal cells were at first unaffected and the keratohyalin and horny layers showed no changes. Subsequently the cells of the lower stratum spinosum and the basal layer underwent a different kind of degeneration; the nuclei and cytoplasm became condensed, the cells became hyalinized and the nuclei fragmented or lysed. Later these basal cells disappeared and the cavity of the vesicle (or pustule) was then immediately adjacent to the dermis.

The fully developed vesicle (Plate 3.4) resembled a plano-convex lens with the following characteristics:

(1) The roof, which was very thin over the summit of the vesicle, consisted of compressed cells of the stratum spinosum, keratohyalin layer and horny layer.

(2) The base consisted at first of cells of the stratum spinosum and basal layer, which showed a hyaline fibrinoid degeneration, becoming swollen, homogeneous and refractile, losing their granular character and staining more intensely with acid dyes. Later they lysed, so that the base of the vesicle was provided by the subjacent dermis.

(3) Since a portion of the cytoskeleton persisted for a long period after the degeneration of the cells of the stratum spinosum, the cavity of the vesicle contained incomplete septa, creating a multiloculated appearance (Plate 3.4A). Such loculation was never complete. Often there were heavier septa, which were made up of the coils of sweat glands traversing the cavity. Like the keratohyalin cells in the roof of the vesicle, the cells of sweat glands appeared resistant to the effects of variola virus.

(4) Fluid accumulated inside the vesicle, with threads of fibrin and a few lymphocytes.

(5) The cells immediately around the vesicle showed decreasing degrees of reticulating degeneration and the basal layers had often proliferated, so that the wall around the vesicle was about twice the thickness of the unaffected epidermis. The rete pegs in the area adjacent to the vesicle were relatively deep.

The pustule

Pustulation occurred by the migration of polymorphonuclear cells from the subpapillary vessels into the vesicle, the dermis being relatively free of such cells (Plate 3.3D and E). This response was not due to secondary bacterial infection; numerous investigations showed that pustules containing abundant leukocytes were bacteria-free. Councilman et al. (1904) commented on the absence of polymorphonuclear leukocytes and the abundance of plasma cells in the adventitial sheaths of the vessels in the dermis as pustulation occurred—evidence of the rapidity and extent of the immune response in ordinary-type smallpox. Unfortunately, the literature lacks descriptions of the histopathology of flat-type smallpox. In such cases one might have expected to find a much less vigorous cellular response at this stage of the disease.

Umbilication

Except on the palms and soles, umbilication was a common feature of the skin lesions in smallpox (see Chapter 1, Plate 1.10). It was apparent quite early, then partially disap-

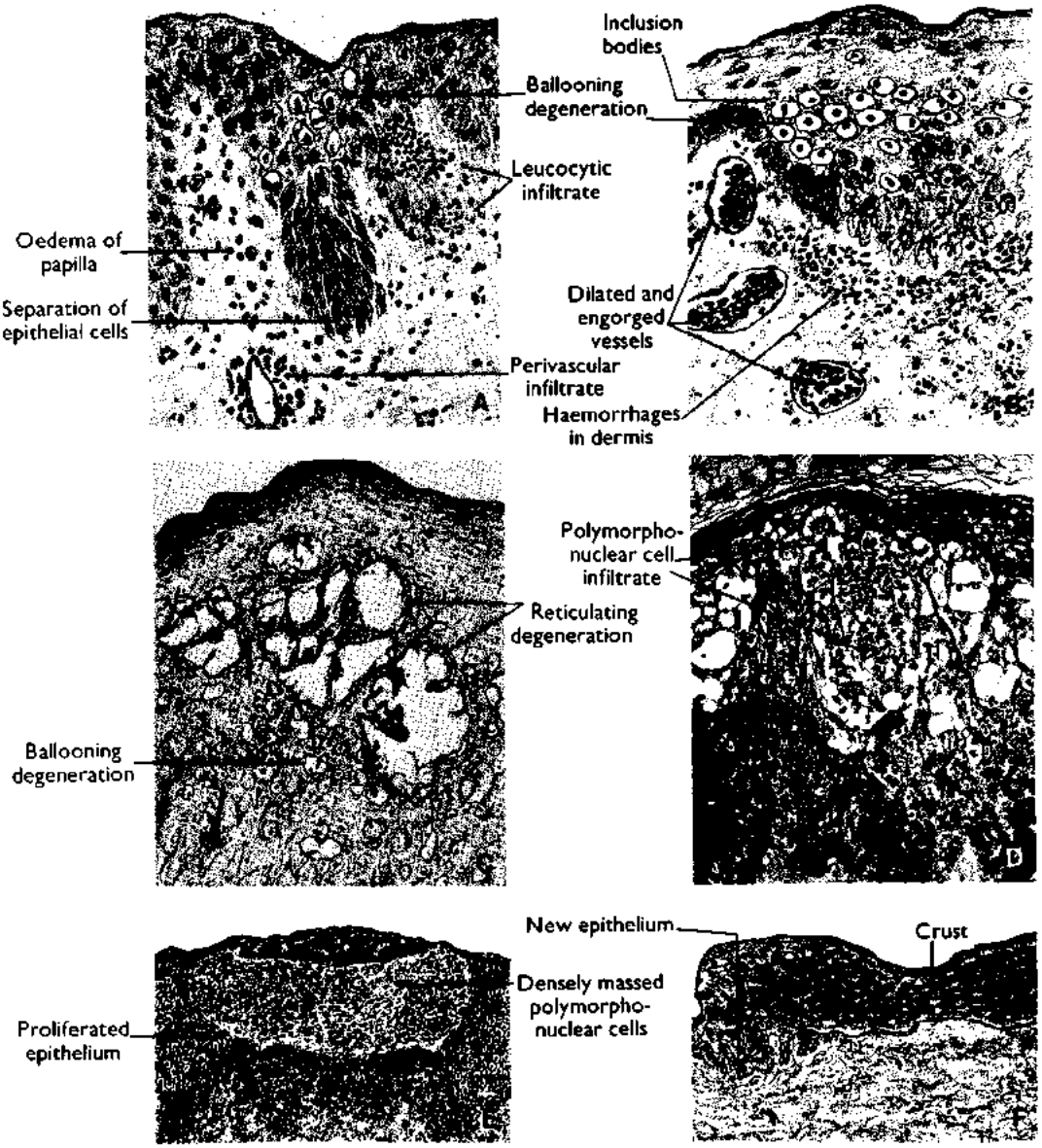


Plate 3.3. Stages in the development and evolution of the skin lesion. **A**: The earliest change was oedema of the dermis leading to the separation of epithelial cells of the papillae and lymphocytic infiltration in the dermis, especially around the small vessels. Ballooning degeneration was seen in a few cells in the lower Malpighian layer. **B**: These changes progressed and the small vessels became dilated and engorged. Inclusion bodies were also visible adjacent to cells showing ballooning degeneration. In early haemorrhagic-type smallpox, illustrated here, there was pronounced haemorrhaging into the dermis. **C**: As the pathological process progressed, the epithelial cells broke down by reticulating degeneration to produce a multilocular vesicle. **D**: The vesicle formed by coalescence of the smaller cavities became infiltrated with polymorphonuclear leukocytes to produce a pustule, around which were cells containing inclusion bodies. **E**: The fully developed pustule became packed with polymorphonuclear leukocytes and the epithelium on either side of the pustule proliferated. **F**: Eventually the pustule became a crust, beneath which new epithelium grew in to repair the surface. Such lesions, in which the sebaceous glands were not involved, healed without leaving a pockmark. (From Michelson & Ikeda, 1927.)

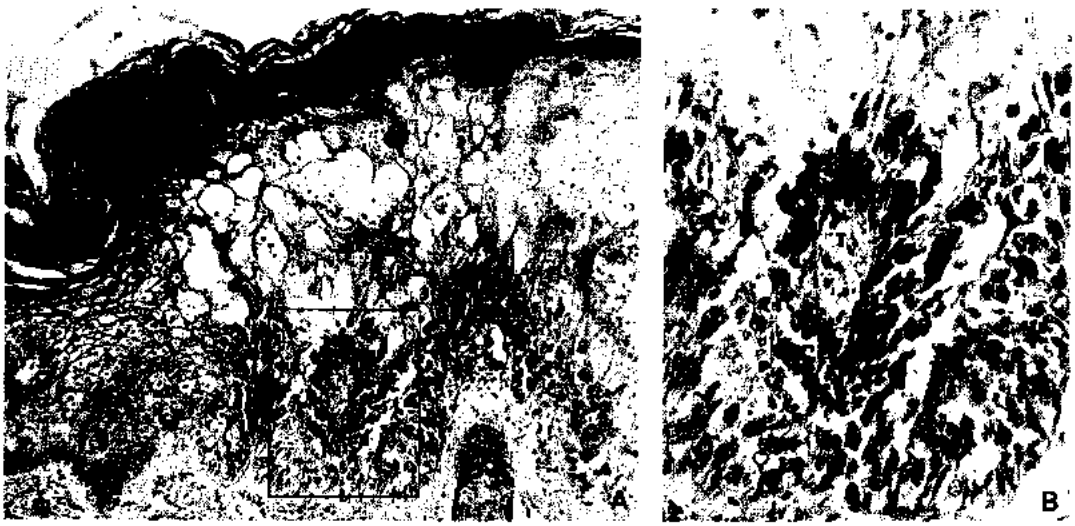


Plate 3.4. Fully developed vesicle. **A**: Loculated cavities with relatively acellular exudate formed as a result of reticulating degeneration of the middle layers of the epidermis. Unaffected keratohyalin and horny layer form the roof of the vesicle; at its base, cells are undergoing hyaline fibrinoid degeneration, which is best seen in **B**, the higher power view. Haematoxylin and eosin, **A** x130; **B** x260. (From Bras, 1952a.)

peared and reappeared during the late stages of pustulation. Umbilication was mainly due to the swelling of the cells around the vesicle and the proliferation of basal cells surrounding the lesion, so that the periphery of the vesicle was raised above the level of its centre, as well as above the surrounding unaffected skin. Often the presence of a hair follicle within a vesicle anchored the centre part, but umbilication was also found in lesions on the lip and glans penis, where no hairs occur. The partial disappearance of umbilication was due to the increase in fluid in the vesicle; as the contents desiccated prior to healing umbilication reappeared.

Scabbing

With the development of an effective immune response, healing began. The contents of the pustule became desiccated and re-epithelialization occurred between the cavity of the pustule and the underlying dermis. The pustular contents became a crust or scab (Plate 3.3 F and Plate 3.5), which was subsequently shed; the newly formed epidermis had no rete pegs. In the absence of secondary infection, the dermis showed very few changes and in most parts of the body the lesions healed without scarring and thus without pockmarks.

In the soles and palms, where the layer of horny cells is very thick, the dried exudate remained enclosed within a mass of horny substance for a long period if not artificially removed.

Scarring

The face bore the heaviest crop of lesions in most cases of smallpox (for example, "semi-confluent" ordinary-type smallpox was the term applied to cases in which lesions were confluent on the face but not elsewhere; see Chapter 1), and lesions usually appeared first on the face and evolved the most rapidly there. However, if the dermis was not involved such lesions should not have produced scars, yet scarring (pockmarks) was very much more common on the face than elsewhere (Ježek et al., 1978d). Bras (1952b) showed that this occurred because sebaceous glands are much larger and more numerous in the facial skin than elsewhere on the body. Although the cells of other skin appendages (hair follicles and sweat glands) were relatively unaffected by variola virus, cells of the sebaceous glands were highly susceptible (Plate 3.6). Degenerative changes began with cytoplasmic hyalinization accompanied by hyperchromatism of the nuclei, karyorrhexis and cytolysis. This degeneration occurred simultaneously in several parts of the sebaceous gland, leading to extensive necrosis in the subepithelial layer of the skin. When healing occurred, the defect in the dermis was filled with granulation tissue, which subse-

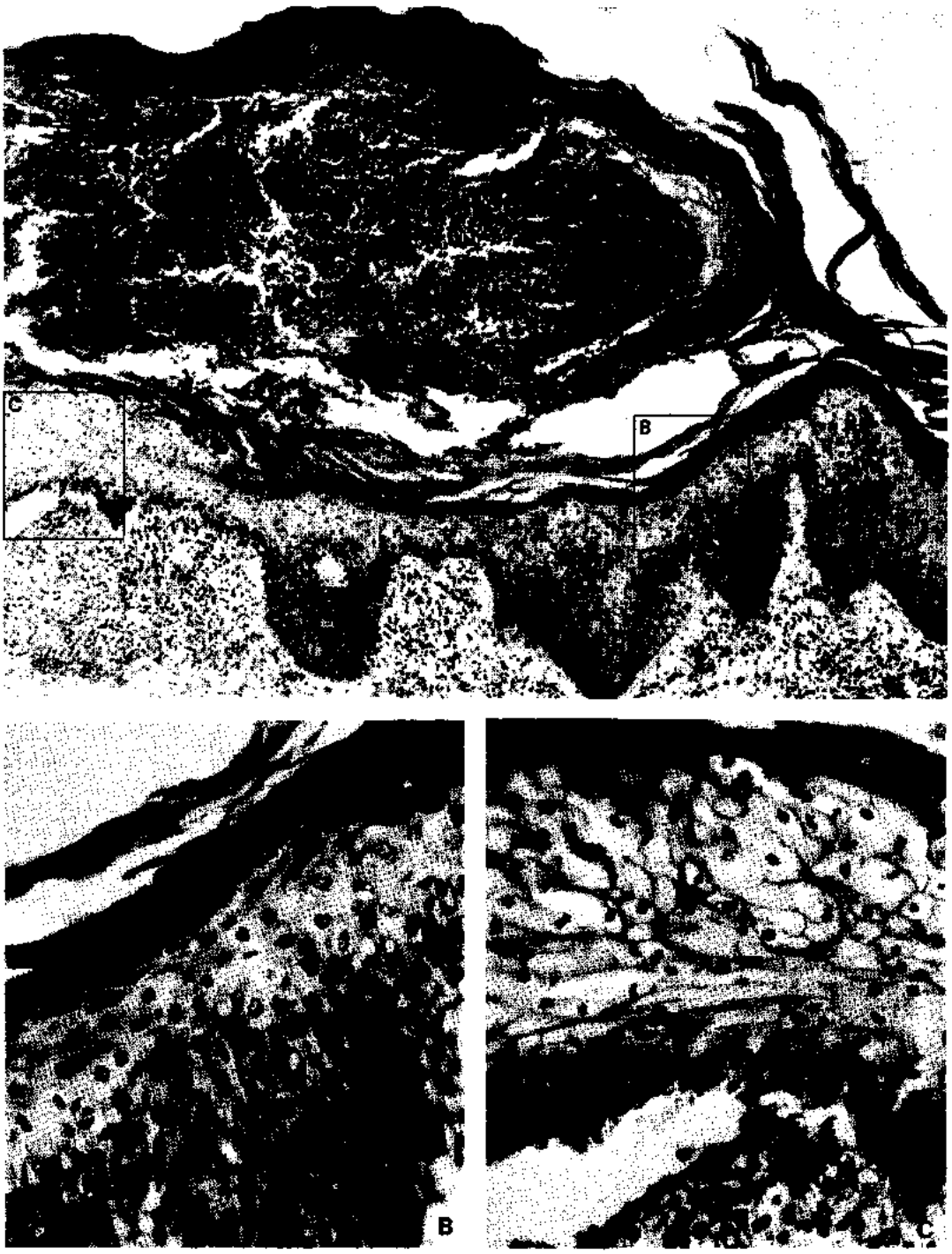


Plate 3.5. Scabbing. **A**: Low-power magnification; the pustule has become a crust. **B** and **C**: High-power magnification. **B**: A keratohyalin layer has developed under the outer part of the pustule. **C**: Recovery is at an earlier stage in the centre; later the keratohyalin layer extends beneath the entire crust. Lesions like this left no scar. (From Bras, 1952a.)

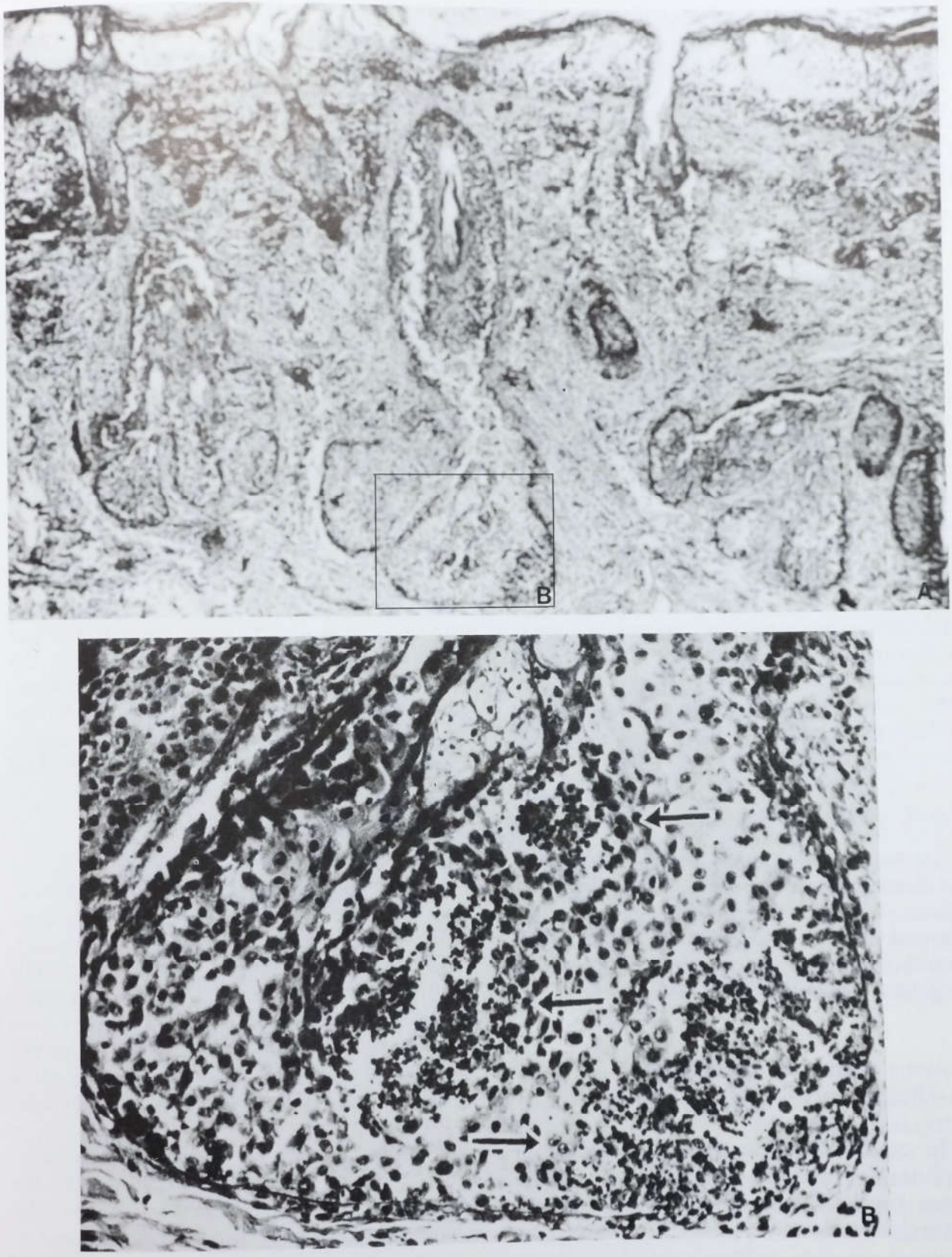


Plate 3.6. Section through pustule on the face; 5th day of rash. **A**: Low-power magnification; there is severe involvement of the subepidermal tissue through necrosis of the large sebaceous glands. **B**: High-power magnification; foci of disintegration in the sebaceous gland are indicated by arrows. Scarring would occur due to fibrosis in the dermis, leading to the formation of a facial pockmark. Haematoxylin and eosin, **A** x50; **B** x225. (From Bras, 1952b.)

quently shrank, leaving localized facial pockmarks.

Descriptions of the histopathology of the skin lesions in variola minor do not include material from the face, since biopsies would be difficult to obtain from this part of the body. It is reasonable to suggest that the rarity of facial pockmarks after variola minor (Ježek & Hardjotanojo, 1980) was due to the failure of variola minor virus to cause the necrosis of cells of the sebaceous glands.

Specific effects of early haemorrhagic-type smallpox

Twenty-three of the 177 cases studied by Bras (1952a) were of early haemorrhagic-type smallpox. In these cases the major difference from the skin lesions just described was the much more extensive hyperaemia of the dermal vessels, which affected the deeper plexuses as well as the subpapillary network. There were also haemorrhages between the collagen fibres of the dermis (Plate 3.3B), and occasionally into the papillae and even the epidermis. Usually the patient died before vesiculation or pustulation occurred. Early reticulating degeneration was usually present in the epidermal cells, which contained large vacuoles. Guarnieri bodies were numerous. The skin lesions were usually extremely diffuse, so that often no normal skin could be found over large areas of the body surface.

Specific effects of late haemorrhagic-type smallpox

Although the skin lesions often seemed to be haemorrhagic pustules (see Chapter 1; Plate 1.23C), histological examination showed that bleeding usually occurred in the dermis beneath the pustule, although some vesicles and pustules did contain erythrocytes.

Lesions of the Mucous Membranes of the Respiratory and Digestive Tracts

In contrast to the skin, in which the evolution of vesicles and pustules was obvious, the lesions of various mucous membranes were less easily observed.

Gross findings

The mucous membranes on which variolous lesions occurred were, in descending order of frequency, the pharynx and uvula (see Chapter 1, Plate 1.3 C), the larynx, the tongue, and the upper part of the trachea and oesophagus (Bras, 1952a). Lesions of the lower part of the trachea and the bronchi were much less frequent, and they were rarely found in the intestines, except for rare cases of haemorrhagic-type smallpox in which the mucous membrane of the lower rectum was shed as a large slough (see Chapter 1). The mucosal lesions evolved more rapidly than those in the skin; healing was usually complete by the end of the 2nd week of illness.

In general, the mucosal lesions of haemorrhagic-type smallpox were similar to those of ordinary-type smallpox in localization and character, except for the more pronounced submucosal haemorrhages. If, as sometimes happened, such patients died soon after the appearance of the skin lesions, the pharyngeal mucosa did not show any gross lesions but was smooth and glistening, with submucosal haemorrhages.

In patients dying at a later stage there was often an adherent pseudomembrane on the lateral wall of the pharynx, which when torn off revealed a haemorrhagic-hyperaemic base. Similar pseudomembranes were found—more rarely—on the epiglottis and larynx, but localized lesions sometimes occurred in the trachea. Ulcers also formed on the tongue, although they were often difficult to see because of the pleats and folds of that organ. Very rarely, circumscribed lesions were found on both surfaces of the intestines.

Histopathology of mucosal lesions

Although showing a general resemblance to the lesions found in the skin, the pathological process in mucous membranes was modified by the nature of the tissue: epithelial cells in mucous membranes are not so tightly packed together as in the skin, and there is no horny layer which might have contained the developing vesicle. There was also a more pronounced exudation of fluid into the subepithelial tissues.

The earliest change in the mucous membranes appeared to be exudation into the epithelium, leading to separation of the cells, which underwent hyaline fibrinoid degeneration. Guarnieri bodies were numerous and numbers of superficial cells were exfoliated from an early stage of development of the lesion. Instead of a vesicle, the extensive necrosis in the epithelial cells, unrestrained by a horny layer, led to early ulceration (Plate 3.7). The base of the necrotic mass of cells was

Plate 3.7. Ulcer on oral mucous membrane. The pustule ulcerates because there is no overlying horny layer. (From Michelson & Ikeda, 1927.)

sharply outlined against the hyperaemic tunica propria. Occasionally the tunica propria showed patchy necrosis unrelated to the superficial defects. Later there was increasing vascularization under the tunica propria and the tissue took on the appearance of granulation tissue, with numerous polymorphonuclear leukocytes in the demarcation zone beneath the necrotic epithelium. This combination produced the pseudomembrane observed macroscopically, which could be easily detached. Because of the numerous bacteria on the mucous membrane of the pharynx the necrotic lesions were usually found to harbour masses of bacteria of various kinds, but this was a secondary phenomenon.

Since the mucosal lesions, especially those of the oropharynx, were the major source of infectious virus in smallpox, it is important to note the time relationships between the development of mucosal and skin lesions. The mucosal lesions appeared during the early papular stage of the rash and had usually healed, without scarring, by the end of the pustular stage.

Although the oropharynx or the respiratory tract is usually regarded as having been the portal of infection in smallpox, no writer has described lesions in the oropharyngeal mucosa, or anywhere in the respiratory tract, which might be regarded as "primary" lesions. The diffuse oropharyngeal lesions, like the circumscribed lesions found on the tongue and uvula, appeared at the same time as the earliest lesions in the skin. There appears to be no reason to doubt that the focal mucosal lesions, like those of the skin, were haematogenous in origin. By analogy with mousepox and rabbitpox, small, non-destructive primary lesions may have occurred in the oral cavity, pharynx or respiratory tract in smallpox, but they would have been impossible to recognize without recourse to a selective staining method such as fluorescent-antibody staining.

Effects on Other Organs

Death was due to viral toxaemia, exacerbated by clotting defects in haemorrhagic-type smallpox. Antibiotics were usually given to all patients in the Madras Infectious Diseases Hospital from the 1950s onwards (A.R. Rao, personal communication, 1981). Such treatment reduced the case-fatality rate by 5–10% in vaccinated subjects, compared with those not given antibiotics, but had no effect on the outcome among unvaccinated patients.

Councilman et al. (1904), Lillie (1930) and Bras (1952a) each described the gross and microscopic appearances of the various internal organs in fatal cases of smallpox. The striking feature about all these reports was the absence of specific lesions anywhere except in the skin and mucous membranes. Readers should refer to these papers for detailed descriptions; comment here is focused mainly on pathological findings that might have been of significance in the pathogenesis of smallpox. Probably the most important change from this point of view was the involvement of the reticuloendothelial system, noted in particular by Bras (1952a).

Reticuloendothelial system

The endothelial cells lining the sinusoids of the liver were often swollen and occasionally proliferating or necrotic. Such changes were most commonly found in individuals who died very early in the course of the disease; Bras suggests that they may have been even more prominent during the pre-eruptive stage. Reticulum cell hyperplasia occurred in the bone marrow and spleen. In addition, the spleen was usually engorged and contained very numerous large lymphoid cells, the morphological sign of a developing immune response. Few specific changes were found in

the lymph nodes, except for small necrotic foci in those of the pharynx and in the tonsils.

Kidneys

Bras (1952a) described spectacular pelvic haemorrhages in cases of early haemorrhagic-type smallpox, a finding which is in accordance with the frequent occurrence of haematuria in these cases.

Testes

Small foci of necrosis occurred in various parts of the testis (parenchyma, mediastinum and epididymis); these were usually too small to be recognized macroscopically.

Liver

Most authors noted that the liver was usually considerably heavier than normal, but found it difficult to ascribe a cause for this; it did not appear to be due to engorgement or fatty infiltration. However, the parenchymal cells usually showed intense cloudy swelling.

Brain

Encephalitis was an occasional complication of smallpox, which occurred much more frequently than did postvaccinial encephalitis after primary vaccination, but it was of minor importance compared with the severe toxaemia of variola major. Encephalitis occurred more often in variola major than in variola minor, but because so few deaths ensued in the latter variety of smallpox it was relatively more important. Marsden & Hurst (1932) provided an exhaustive review of the literature and gave detailed histories of 11 cases occurring after variola minor, of which 3 were fatal. The fatal cases had brain lesions like those described for postvaccinial encephalitis (see below).

Effects specific to haemorrhagic-type smallpox

As well as the extensive haemorrhages in the skin found in all cases of haemorrhagic-type smallpox, both early and late, haemorrhages were often found in other sites, such as the gastric mucous membrane, the pelvis of the kidney, the myocardium and endocardium, and the submucosa of the pharynx and larynx.

Although megakaryocytes were numerous in the bone marrow of cases of pustular smallpox, there were strikingly few present in the bone marrow of primary haemorrhagic-type smallpox, a finding which explains the profound thrombocytopenia and bleeding that occurred in these cases (see Chapter 1).

THE HISTOPATHOLOGY OF VACCINIA AND VACCINIAL COMPLICATIONS

Clinical aspects of vaccination and revaccination and the complications associated with vaccination are described and illustrated in Chapter 7. Numerous studies have been carried out on the histology of cutaneous changes in vaccinated calves and rabbits (reviewed by Lillie, 1930) but few studies have been made in man. The most important complication of vaccination, postvaccinial encephalitis, has been studied by many investigators, but its pathogenesis remains obscure.

Normal Vaccination

The aim of vaccination was to bring vaccinia virus into contact with cells in the Malpighian layer of the epidermis. After primary vaccination a papule developed in 3–5 days, rapidly became a vesicle and later became pustular, reaching its maximum size after 8–10 days (see Fig. 3.1). A scab was then formed, which separated at 14–21 days, leaving the typical vaccination scar.

Vaccination produced a generalized infection in man, with swelling and tenderness of the draining lymph nodes and a viraemia sometimes detectable between the 3rd and the 10th day after vaccination, most frequently on the 6th day (Herzberg-Kremmer & Herzberg, 1930a,b; Siegert & Schulz, 1953). Gins et al. (1929) recovered vaccinia virus from tonsillar swabs taken 3, 4 and 5 days after vaccination, and Gurvich et al. (1979) reported the isolation of vaccinia virus from the pharyngeal swabs of 49% of children with postvaccinial tonsillitis between the 7th and the 15th day after vaccination, compared with 7% of children with uncomplicated vaccinia and no evidence of pharyngitis. The level and persistence of detectable viraemia were dependent on the strain of virus used; it was regarded as rare and transient by Blattner et al. (1964) and Kempe (1960), who used the mild New York City Board of Health strain. More

prolonged viraemia occurred in children with immunological deficiencies (Keidan et al., 1953), some of whom suffered from progressive vaccinia.

Changes in the skin

Howard & Perkins (1905) studied the histological appearance of vaccination lesions in biopsies taken from 12 subjects. The earliest changes were cytoplasmic and perinuclear vacuolation in the epithelium, accompanied by cloudy swelling, coagulation necrosis, intercellular oedema and vesicle formation. Within 48 hours, a cup-shaped vesicle traversed by an eosinophilic reticular network had appeared, of which the stratum corneum formed the roof, and the floor, centrally, was bare dermis. At the sides were cells in hyaline degeneration, which were intensely eosinophilic, with shrunken pyknotic nuclei. There were marked oedema of the papillae and free erythrocytes, mononuclear and polymorphonuclear cells, as well as perivascular infiltration. Subsequently, leukocytes invaded the vesicle, and the necrosis of epithelium and leukocytes produced a crust of dense, homogeneous, deeply staining reticulum. Guarnieri bodies were present in the epithelial cells. Epithelial outgrowth occurred beneath the crusts.

In progressive vaccinia the primary vesicle failed to heal and the usual lymphocytic infiltration failed to occur because the persons involved had defective cell-mediated immune responses. In one such case, Keidan et al. (1953) noted that germinal centres and lymphocytes were completely absent from the axillary lymph node and spleen of the patient, although many plasma cells were present (Plate 3.8).

Plate 3.8. Section of a vesicle produced in human skin by vaccinia virus inoculated in a child who developed progressive vaccinia. There are no inflammatory cells in the dermis. (From Keidan et al., 1953.)

The draining lymph nodes

Successful primary vaccination produced moderately enlarged, painful regional lymph nodes. This reaction was first apparent on about the 5th day as the skin lesion became vesicular, and most pronounced on about the 10th day. The lymph nodes often remained enlarged and tender for 2–4 weeks after the skin lesion had healed.

In 2 persons who had been killed in an accident while at the height of a primary vaccinial reaction, it was noted (W.E.D. Evans, unpublished observation, 1960—cited by Symmers, 1978) that the axillary lymph nodes showed marked follicular hyperplasia with large germinal centres. There was a conspicuous proliferation of large pale cells among the lymphocytes of the cortical and paracortical regions—morphological indicators of an active immune response—and Guarnieri bodies were seen in one case.

A rare sequel of vaccination, persistent lymphadenitis, was sometimes confused with lymphoma if biopsies were performed for the diagnosis of painless lymphadenopathy. Hartsock (1968) records that a diagnosis of malignant lymphoma was mistakenly made in 9 out of 20 such cases; all eventually subsided completely. The lymph nodes in these cases showed diffuse or follicular hyperplasia, an increased number of reticular lymphoblasts, which gave a mottled appearance to the sections, and a mixed cellular response, with varying numbers of eosinophils, plasma cells and mast cells. The morphological changes in

the lymph nodes indicate a vigorous immune response to vaccinial infection.

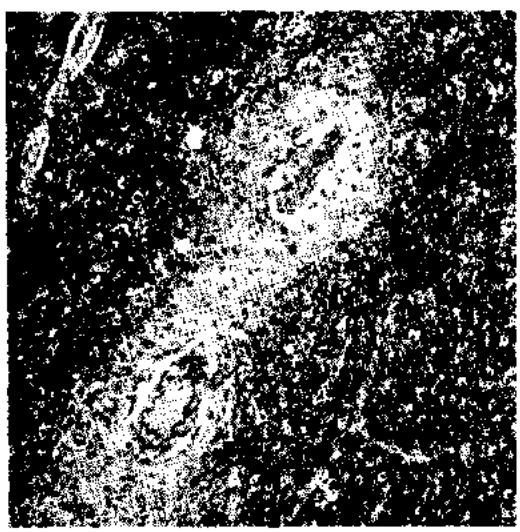
Postvaccinial Encephalitis

The incidence and clinical features of this rare but important complication of vaccination are described in Chapter 7. Postvaccinial encephalitis (or encephalomyelitis) is characterized by acute perivascular demyelination. Similar lesions sometimes occurred after smallpox (Marsden & Hurst, 1932). Postinfection encephalitis is a well-recognized complication of measles and varicella and a similar disease sometimes occurs after vaccination against rabies. One case has been recorded as a complication of cowpox in a human being (Verlinde, 1951). The histopathology of postinfection and postvaccination encephalitis, from whatever cause, is identical.

Although Kaiser & Zappert (1938) noted that 35 cases of disease of the central nervous system were recorded among 10 090 persons vaccinated in Bohemia in 1801 and 1802, postvaccinial encephalitis was not recognized as a serious problem until the 1920s. The first clear account of the clinical picture and histological changes was given by Turnbull & McIntosh (1926). After that time physicians became more aware of its occurrence and postvaccinial encephalitis presented a serious problem, especially in some European countries, in the period between 1930 and 1960 (see Chapter 7).

The onset of nervous symptoms, which were predominantly encephalitic or myelitic, was abrupt and took place 10–13 days after vaccination—i.e., at a time when both the cell-mediated and humoral immune responses were well developed. A striking feature was the astonishingly rapid and complete recovery of apparently moribund subjects, but the case-fatality rate was usually between 25% and 50%.

Vries (1960) distinguished two pathological groups, which he characterized as postvaccinial encephalopathy in infants, and postvaccinial encephalitis in older persons. In infants under 2 years of age the changes seen in the brain were essentially vascular: oedema, either general or perivascular; mild lymphocytic infiltration of the meninges and some perivascular spaces; widespread degenerative changes in the ganglion cells; and sometimes perivascular haemorrhages. Older persons exhibited the features characteristic of all postinfection encephalitides, as described by Turnbull & McIntosh (1926) and reviewed by Hurst (1953). Meningeal inflammation was slight and irregular; the nerve cells were little affected; and advanced neuronophagia did not occur. The dominant feature was perivascular demyelination of the medullary sheaths, accompanied by destruction of the axis cylinders (Plate 3.9). The perivascular space contained many lymphocytes and the demyelinated areas contained lymphocytes and highly pleomorphic microglia. Conybeare (1964b) and a number of Soviet authors confirmed the differentiation between encephalopathy in



R.T. JOHNSON

G. BRAS

Plate 3.9. Lesions in the brain in postvaccinial encephalitis. **A**: Perivascular demyelination. **B:** Perivascular cellular infiltration.

infants and postvaccinial encephalitis in older persons, although in older infants the conditions merged and early perivascular demyelination was seen.

Although vaccinia virus was occasionally demonstrable in the brain or cerebrospinal fluid (Turnbull & McIntosh, 1926), most investigators failed to recover virus from the brains of fatal cases. Kurata et al. (1977), for example, were unable to recover vaccinia virus from any of 5 reported fatal cases, or from 30 other cases examined during the previous 20 years. However, they demonstrated vaccinial antigen in the leptomeninges and, complexed with IgM, in the areas of perivascular cellular infiltration in 3 out of the 5 cases studied. The consensus is that apart from postvaccinial encephalopathy in infants, all the postinfection encephalitides, whether occurring as a result of smallpox, vaccination, measles or other viral infections, are essentially an allergic response to some viral or virus-induced antigen(s) (Johnson, 1982).

The most puzzling feature about postvaccinial encephalitis in persons over 2 years of age was the great variability in its frequency in different countries and at different times (see Chapter 7). There appears to have been some relationship between the virulence of the virus (variola or vaccinia) and the frequency of postinfection encephalitis. Rao (1972) observed frequencies of 1 in 500 variola major cases and 1 in 100 000 primary vaccinations in Madras, and Marsden (1936) 1 in 2000 cases of variola minor in London. The incidence after primary vaccination in different countries and at different times varied from 9 per million in the USA in 1968 to 1219 per million in Austria for the period 1948–1953 (see Chapter 7, Table 7.8). In several countries in which the incidence was high the rate fell substantially when the strain of virus used for vaccination was changed.

Postinfection encephalitis in smallpox and after vaccination was clearly due to an unusual host response, probably to poxvirus antigens or antigen–antibody complexes that localized in neural tissue. It is significant that postvaccinial encephalitis was almost unknown as a complication of revaccination, an observation which led to the promotion in the 1960s of a variety of schemes of "preimmunization" in countries from which smallpox had been eliminated (see Chapter 7). The likelihood of neural localization of the relevant antigen was, in part, determined by the virulence of the virus concerned, there being a gradation in frequency: variola major, variola minor, more virulent strains of vaccinia virus, less virulent strains of vaccinia virus.

VIRAL PERSISTENCE AND REACTIVATION

Different viruses of vertebrates behave in characteristic ways after the host animal recovers from an acute infection, and the precise mode of behaviour has important epidemiological implications. Five situations can be distinguished:

(1) The acute infection is followed by clinical recovery and the virus is completely eliminated from the body; it cannot therefore be reactivated by immunosuppression or any other means, because it is no longer present in the host organism. Mumps and poliomyelitis are examples. The smallpox eradication campaign was undertaken on the assumption that smallpox also fell into this category.

(2) The acute infection is followed by clinical recovery but the virus persists in the body. It may be reactivated by a variety of stimuli and can then cause recurrent illness, with the shedding of virus. This is the characteristic mode of behaviour of herpesviruses—e.g., in herpes simplex, varicella-zoster and cytomegalovirus infections.

(3) The infection is followed by clinical recovery and in the vast majority of individuals the virus is completely eliminated. Occasionally, however, it may persist and cause chronic disease, but it persists in a sequestered site and is not shed, so that persistence is of no epidemiological significance. Measles, with its rare complication, subacute sclerosing panencephalitis, is a good example.

(4) The infection is usually inapparent, but virus may persist in sequestered sites for long periods without ever causing symptoms, unless it is reactivated by procedures such as renal transplantation. Certain human papovaviruses behave in this way (Gardner, 1977); they may also be reactivated and excreted in urine during normal pregnancy, with no harmful effects (Coleman et al., 1980).

(5) After the patient has recovered from the acute infection the virus persists as a chronic infection which may sometimes be associated with chronic disease. Such cases may be infectious; hepatitis B is an example.

From the point of view of the smallpox eradication programme, the question of viral

persistence was of importance from two points of view. First, if reactivation and re-excretion of virus could occur in a person who had recovered from smallpox, under any circumstances, such a person would constitute a potential source from which smallpox could re-emerge. Secondly, the likelihood of success in a search for virus in an animal reservoir of variola or monkeypox viruses is greatly influenced by whether these viruses persist in the tissues of infected animals for prolonged periods. If it occurred, persistent infection could be of epidemiological importance in human monkeypox (see Chapter 29), for persistent virus, even if it were not excreted, could be a source of infection to humans handling or eating such animals.

Persistence of Variola Virus in Human Patients

The evidence against the persistence of variola virus in man, after recovery from infection, is strong but circumstantial; it is impossible to prove that cases of persistent infection never arose. In the whole history of smallpox, no case has occurred which could be unequivocally traced back to infection acquired from a person who had recovered from the disease months or years earlier, nor has any suspicion of the recurrence of symptoms or of the circulation of variola virus ever arisen in a person who had recovered from smallpox and subsequently undergone immunosuppressive treatment. Nor has vaccinia virus, used until recently on a large scale in Europe and North America (where immunosuppression therapies are practised more widely than in the developing countries), ever shown any indication that it could cause a latent infection in man. Since alert clinicians and virologists have recognized the occurrence of latent infections with a wide variety of viruses, and their reactivation after immunosuppressive treatment, this negative evidence is important. It is reasonable to agree with the conventional belief that variola virus belonged to the first group of viruses listed—i.e., infection was followed by death or recovery with complete elimination of the virus; persistent infection did not occur.

Persistence of Orthopoxviruses in Animals

The evidence that some orthopoxviruses might persist for long periods after recovery from infection in various animal species is more difficult to evaluate than the persistence of variola or vaccinia viruses in man.

Mousepox

Several authors have suggested that ectromelia virus could produce a latent infection in mice, but most examples that have been quoted could be explained as plausibly by persistent infection in the population, rather than prolonged viral persistence in individual mice. However, there are a few examples of the persistence of ectromelia virus for at least several weeks in a sequestered site in healthy mice and also of persistent infection with shedding. For example, Fenner (1948c) noted the recurrence of foot swelling, and the isolation of virus from the swollen foot, in 2 mice that had been infected 2 and 7 months earlier and had not been subsequently exposed to infection. In other experiments Fenner (1948d) demonstrated the presence of ectromelia virus in the lungs and spleen of 2 mice that had recovered from infection acquired about 45 and 93 days earlier; 112 other mice that were tested more than 5 weeks after recovery gave negative results. There was no evidence that such mice shed virus. However, because mouse tissues or tumours are passaged in other mice, such persistent infections, especially if they occurred in animals that had just recovered from a mild or inapparent infection, could constitute a source for the dissemination of mousepox (see *Laboratory animal science*, 1981).

A more significant observation in relation to possible persistent infection with orthopoxviruses was that recorded by Gledhill (1962a,b), who demonstrated that mice infected by the oral route could sustain a chronic infection of the intestinal tract, with excretion of virus in the faeces and scabs on the tail near the anus. He was unable to "activate" acute mousepox in such carriers, nor did they cause infection in susceptible mice placed in the same cages.

Isolation of other orthopoxviruses from naturally infected normal animals

A number of reports of the recovery of orthopoxviruses from the tissues of apparently normal animals have been published (Table 3.3). There are two problems in evaluating the significance of these findings, in terms of persistent infection. First, it is

Table 3.3. Recovery of orthopoxviruses from tissues of healthy animals thought to have been naturally infected[a]

Example No.	Virus	Circumstances
1(i)	Cowpox (rat strain)[b]	From lungs of 5 and kidneys of 14 out of 113 white rats in an interepidemic period.
1(ii)	Cowpox (Turkmenia strain)[c]	From kidneys of great gerbil (*Rhombomys opimus*) and yellow suslik (*Cicellus fulvus*) captured in Turkmenistan, USSR.
2	Monkeypox[d]	From kidneys of several apparently healthy cynomolgus monkeys that had been exposed to infection in an outbreak in a laboratory colony.
3	Taterapox[e]	From liver/spleen suspension of 1 of 95 wild *Tatera kempi* captured in Benin.
4	Ectromelia[f,g]	From brains of apparently normal mice in a colony enzootically infected with ectromelia virus.
5(i)	Vaccinia[h]	Rabbitpox virus recovered from kidney of an apparently healthy *Macaca rhesus*.
5(ii)	Vaccinia[i]	Vaccinia virus recovered from kidney of *Cercopithecus ascanius* killed in Zaire.

[a] Excluding "whitepox" viruses (see Chapter 30, Table 30.2).
[b] Marennikova (1979); Shelukhina et al. (1979b).
[c] Ladnyi et al. (1975); Marennikova et al. (1978b).
[d] Magnus et al. (1959).
[e] Lourie et al. (1975).
[f] Schell (1964).
[g] Topciu et al. (1972).
[h] Alekseeva & Akopova (1966).
[i] Shelukhina et al. (1975).

Table 3.4 Recovery of orthopoxviruses from animals that had been experimentally infected some weeks earlier and showed no clinical signs at time of recovery of virus

Example No.	Virus	Circumstances
1	Ectromelia[a]	From lungs and spleen of 2 out of 114 mice tested 5 weeks or more after recovery.
2	Monkeypox[b]	From kidneys and lungs of hamsters up to 6 weeks after intracardiac injection.
3	Cowpox[b]	From kidneys and lungs of cotton rats and rats inoculated intranasally up to 6 weeks earlier.
4	Cowpox (rat strain)[b,c]	From several organs of white rats and *Rattus norvegicus* inoculated intranasally 4 weeks earlier.
5	Cowpox (Turkmenia strain)[d]	From kidneys and testes of great gerbils and yellow susliks inoculated 5 weeks earlier.
6	Vaccinia[e]	From spleen and testes of rabbits inoculated intradermally with neurovaccinia virus 114 and 133 days earlier.
7	Vaccinia[f]	From brains of mice pre-treated with cyclophosphamide 60 days after inoculation with vaccinia virus; by co-cultivation only.
8	Variola[g]	From brains of mice that had been inoculated intracerebrally as infant mice up to 62 days earlier.

[a] Fenner (1948c).
[b] Shelukhina et al. (1979b).
[c] Maiboroda (1982).
[d] Marennikova et al. (1978b).
[e] Olitsky & Long (1929).
[f] Ginsberg & Johnson (1977).
[g] Sarkar et al. (1959).

possible that most or all of the positive results were obtained with animals that were experiencing an inapparent infection at the time or were convalescing from infection (examples 1(i), 1(ii), 2, 3 and 4 of Table 3.3). Secondly, the virus apparently isolated from a normal animal may have been a laboratory contaminant (examples 5(i) and 5(ii) of Table 3.3).

Isolation of orthopoxviruses from "normal" animals after recovery from experimental infection

Although most investigators have failed to demonstrate persistent infection with orthopoxviruses, there are several reports of the recovery of orthopoxviruses from the tissues of laboratory animals that had been infected several weeks earlier and were apparently normal at the time of isolation of the viruses (Table 3.4). The results with mousepox have been described. The most systematic studies were those reported by Marennikova and her colleagues with monkeypox and cowpox viruses (examples 2–5 of Table 3.4). The animals suffered inapparent infections and the relevant virus was recovered from some animals for up to 6 weeks after inoculation, when the experiment was terminated. Great

gerbils and yellow susliks suffered severe disease with high mortality after inoculation with the Turkmenia strain of cowpox virus, but virus could be recovered from the kidneys and testes of animals that survived for 5 weeks (example 5, Table 3.4).

Positive results were also reported with vaccinia virus in rabbits and mice (examples 6 and 7, Table 3.4) and variola virus in mice (example 8, Table 3.4).

Epidemiological Significance

It is difficult to assess the epidemiological significance of these observations. Only in Gledhill's experiments with ectromelia was there any evidence that virus shedding occurred, but even then the infection of susceptible contact mice was not observed (Gledhill, 1962a,b). In all other cases the virus was in a sequestered site and its presence was revealed only by laboratory manipulations. It is reasonable to suggest that the persistent carriage and shedding of virus is not a factor of epidemiological significance in orthopoxvirus infections in the way that is so important in arenavirus and herpesvirus infections.

With smallpox, there is a further epidemiological observation of great significance. Over a period of some 50 years, during this century, smallpox was progressively eliminated from every country in the world. In no instance was a "spontaneous" outbreak identified after smallpox had been eliminated from a region or country. All outbreaks of which the source was found could be traced to the introduction of virus from known infected areas by known infected individuals.

These results are also relevant to the searches for the natural reservoir animal or animals of monkeypox in Africa (see Chapter 29) and the claims that variola virus has been isolated from various healthy primates and rodents (see Chapter 30). It is clear that orthopoxviruses have only very rarely been recovered from wild animals, even when tests were carried out in areas and with species in which there was serological evidence that orthopoxvirus infection was widespread. It is likely that virus isolation in such circumstances usually depends on the chance selection of an animal suffering or convalescing from infection rather than a long-term carrier. This appears to have happened with rodent strains of cowpox virus (examples 1(i) and 1(ii) of Table 3.3). The chance of catching such an animal during an ecological survey in tropical forest areas, with their abundance and diversity of animals, is quite small, which may account for the failure so far to recover monkeypox virus from a wild animal (except in one instance from a sick squirrel), and in part for the rarity of cases of human monkeypox.

THE IMMUNE RESPONSE IN SMALLPOX AND AFTER VACCINATION

Variolation, the ancient practice whereby smallpox was transmitted to a susceptible person by the inoculation of material from smallpox scabs or vesicles, was based on observations that pockmarked persons never suffered from smallpox a second time. It provided the foundation on which the science of immunology was built (Needham, 1980). The next major landmark in immunology, as Pasteur (1881) recognized when he generalized the use of the term vaccination, was Jenner's substitution of an antigenically related non-virulent agent (cowpox/vaccinia virus) for the virus of smallpox.

Although immunology arose from observations of protection from infection or reinfection, the immune response also plays an important role in the process of recovery in an infected person. In the following pages both aspects are reviewed.

Protection against Reinfection

After vaccination

The responses obtained on revaccination with vaccinia virus at various intervals after primary vaccination or earlier revaccination are described in Chapter 7. Immunity may be manifested by a complete absence of reactivity, by an allergic reaction or by an accelerated reaction which may nevertheless progress to vesiculation and which involves at least local replication of the virus used for revaccination. Skin site appears to play a role in the severity of the response to revaccination. In India revaccination was often performed on the ventral surface of the forearm because positive reactions were more frequently obtained there than in revaccination over the deltoid muscle. Even more striking were the finger lesions sustained by workers in vaccine production laboratories, who often

Cells Involved in the Immune Response

The immune response is a complicated process about which a great deal has been discovered since most of the work on immunological responses in smallpox and vaccinia was carried out. Understanding of cell-mediated immunity, in particular, has burgeoned in recent years. A summary of current views on the cells involved in the immune response as they relate to viral infections is shown in Fig. 3.4.

Very briefly, three types of cell are involved - macrophages and two types of lymphocyte. Certain kinds of macrophage process antigens for presentation to lymphocytes. Lymphocytes belong to two main classes: T cells (meaning thymus-derived cells, of which there are several subclasses), and B cells (coming mainly from the bone marrow in mammals), which produce antibodies. B cells have antibody-like receptors on their surfaces, one or a few cells having receptors of every imaginable specificity. When an antigen is appropriately presented to such a cell by a macrophage, the B cell differentiates to form an antibody-synthesizing plasma cell and at the same time divides to form a population (clone) of identical cells. Later, some members of this clone are sequestered as long-lived memory B cells, which are of critical importance in mounting a secondary response when reinfection occurs.

T cells have different kinds of antibody-like receptors on their surface, and they also react specifically to different antigens, expand clonally, liberate active substances called lymphokines, and sequester a small proportion of each clone as long-lived memory T cells. There are several subclasses of T cells. Two of these modulate the activity of the antibody-producing B cells and of other T cells: Th or helper T cells and Ts or suppressor T cells. Other kinds of T cells are responsible for the two main components of the cell-mediated immune response: Tc or cytotoxic T cells, which actively destroy cells bearing complementary virus-induced antigens on their surface, and Td cells, which differentiate on contact with the specific antigen, release lymphokines and produce delayed hypersensitivity reactions. T cells also produce one class of interferon (gamma-interferon), and there is another poorly understood class of lymphocytes (natural killer (NK) cells), which appear to kill certain host cells non-specifically.

suffered from vaccinial whitlows in spite of the fact that they were revaccinated annually (Horgan & Haseeb, 1944). Such cases often exhibited enlargement of the epitrochlear and axillary lymph nodes and sometimes the reinfection progressed like a primary vaccinial reaction, with maximum vesiculation on the 9th or 10th day.

After smallpox

It is obviously difficult to obtain precise figures on the incidence of second attacks of smallpox. Dixon (1962), quoting from the observations of Barry (1889) in Sheffield, and Rao (1972), whose views were based on his own experience supported by laboratory evidence, suggested that about 1 in 1000 pockmarked persons suffered a second attack of smallpox. Epidemiologists working in the field during the Intensified Smallpox Eradication Programme believed that this figure was rather high. Although collectively they saw many thousands of cases of variola major, it was very rare indeed to find one in a pockmarked person.

Heterologous protection

Depending on the closeness of the antigenic relationship and the degree of generalization of the infection (and thus the intensity of the immune response), homologous protection would be expected to be greater than protection induced by a heterologous agent. Experiments in animals reveal that infection with any one orthopoxvirus produces substantial protection against disease produced by any other orthopoxvirus (vaccinia virus against ectromelia in mice: Fenner, 1947a; ectromelia virus against rabbitpox in rabbits: Christensen et al., 1967; vaccinia virus against monkeypox in monkeys: McConnell et al., 1964; vaccinia virus against cowpox in rab-

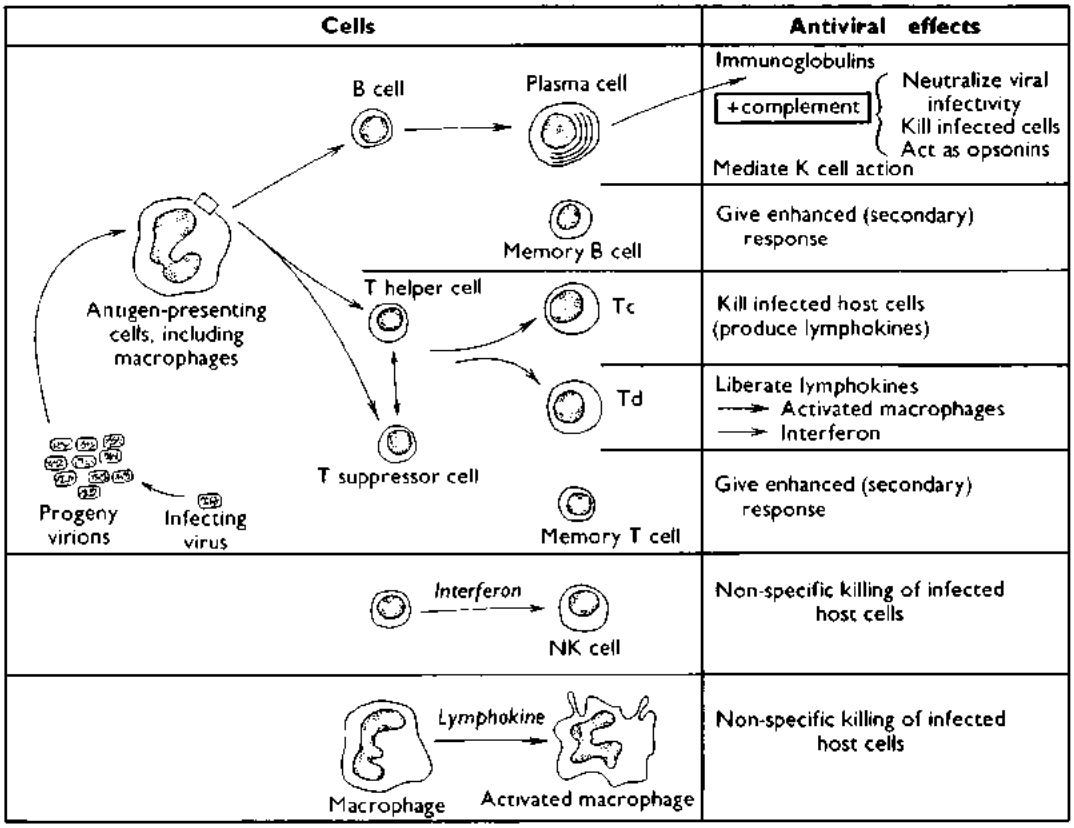


Fig. 3.4. Cells involved in antiviral immune response. Tc = cytotoxic T cell; Td = delayed hypersensitivity T cell; K cell = killer cell; NK cell = natural killer cell.

bits: Downie, 1939b; vaccinia virus against variola in monkeys: Horgan & Haseeb, 1939; taterapox virus against monkeypox in monkeys: Lourie et al., 1975). Likewise, a prior attack of smallpox gave some protection against vaccination with vaccinia virus, which was much less prolonged after variola minor than after variola major (see Chapter 1, Table 1.10). Persons with active variola major, vaccinated in order to prevent smallpox infection in case of a misdiagnosis, never exhibited a major reaction (Zikmund et al., 1978).

However, the classic example of cross-protection, on which the success of the global eradication campaign depended, was that described by Jenner (1798). Although Jenner realized that cowpox inoculation did not always result in a take (Jenner, 1799, 1804), he maintained that successful vaccination produced lifelong immunity to smallpox. That view was clearly wrong, and revaccination became an accepted practice early in the 19th century in continental Europe, although it was not widely practised until much later in Great Britain. Detailed information on the persistence of immunity to smallpox after vaccination with vaccinia virus is presented in Chapters 1 and 7. In general, vaccination within the previous 5 years protected persons exposed to smallpox against clinical disease and some protection was evident for over 30 years. In countries in which smallpox was endemic, estimation of the duration of protection was complicated by the fact that subclinical smallpox, recognizable by rises in the titre of complement-fixing antibodies (which persist for only a few months after infection), occurred in a substantial number of vaccinated individuals who were in close contact with cases of smallpox (Heiner et al., 1971a; see Chapter 1).

Humoral and Cellular Responses in Orthopoxvirus Infections

In orthopoxvirus infections the humoral response may result in the production of short-lived IgM or persistent IgG, and it may

be elicited by inactive virions or viral antigens and by both non-enveloped and enveloped infectious virions. The cellular response also may be evoked either by inactive antigens (which result in delayed hypersensitivity reactions without cytotoxic effects) or by cell surface membranes altered by viral infection, when both cytotoxic responses and delayed hypersensitivity may be involved.

In the analysis of the scientific literature which follows, the humoral and cellular immune responses will be discussed separately; however, in any animal inoculated or infected with viral antigens or virus preparations, the reactions described, and many others, go on simultaneously. In each section technical methods will be described first and then the results of experiments on orthopoxvirus infections in laboratory animals and on smallpox and vaccinia in man will be reported.

Methods for Measuring Antibodies to Orthopoxviruses

At various times almost every method that has been developed for detecting antibodies has been employed for titrating antibodies to orthopoxviruses, especially in the case of vaccinia virus, the prototype virus of the genus. In the following paragraphs the methods more commonly used are listed, with comments about particular features of each, notably its sensitivity, the persistence of the antibodies detected by particular tests, the potential of the test for distinguishing between different species of orthopoxvirus, and the relation of antibodies detected by various tests to protection.

With the discovery of monoclonal antibodies and the subsequent development of this new tool, serological methods achieved a quantum leap in their power to detect and discriminate between antigenic sites (epitopes). In principle, monoclonal antibodies can be used to titrate either antigens, by any of the methods outlined below, or antibodies, by using them in blocking tests. At the time this chapter was written no use had been made of monoclonal antibodies in orthopoxvirus research.

Sensitivity and specificity of different serological tests

Different serological tests differ considerably in both sensitivity—i.e., the amount of antibody required to give a positive result—and specificity—i.e., their ability to discriminate between different but related antigens. Although they can be refined, if used with monoclonal antibodies or with antibodies produced by immunization with purified antigens, the first four tests described below ordinarily register reactions between several or all of the large number of antigens produced in orthopoxvirus infections and certain classes of all the antibodies, of varying specificity, that are produced during immunization or infection. Other serological tests are more discriminative, in that they involve only one or a few of the antigens produced during viral infection and the corresponding antibodies, or else the mixed antigen–antibody complexes can be separated by diffusion or electrophoresis in gels.

Complement-fixation (CF) test

Many poxvirus antigens react in CF tests, including an early antigen located on the surface of vaccinia-infected cells (Ueda et al., 1972). However, only antibodies of certain classes and subclasses (in man: IgM and to a lesser extent IgG_1, IgG_2 and IgG_3) participate in CF reactions; in general, such antibodies are short-lived so that a positive CF reaction is an index of recent infection (in man, within 12 months; Wulff et al., 1969). This property was exploited by Heiner et al. (1971a) in their study of subclinical infections in vaccinated household contacts of smallpox cases (see Chapter 1, Fig. 1.2).

Because so many antigens are common to all orthopoxviruses, the CF reaction is useless for discriminating between different species of the genus, unless used with an antigen that is species-specific.

Immunofluorescence test

Like the CF test, immunofluorescence can be used to detect many different orthopoxvirus antigens. However, in contrast to the antibodies active in complement fixation, the IgG antibodies involved in immunofluorescence reactions are long-lived (Gispen et al., 1974). Combined with serial absorptions of antisera with suitable suspensions of virus-infected tissue, immunofluorescence can be used to recognize species-specific orthopoxvirus antibodies in sera of animals caught in the wild (Gispen et al., 1976). However, it suffers from the disadvantage of being relatively insensitive. Immunofluorescence has proved useful in the study of the sequence of intracellular events in orthopoxvirus infec-

tions (Ueda et al., 1972) and in studies of the pathogenesis of poxvirus infections in experimental animals (Mims, 1964, 1966), for it provides a method of demonstrating the cellular and intracellular localization of viral antigens.

Radioimmunoassay

The sensitivity of several serological methods can be greatly enhanced by tagging relevant antigens or antibodies with radioisotopes. Radioimmunoassay, which is about a thousand times more sensitive than immunofluorescence, for example, can be used for the detection of antigen antibody reactions in tubes or plates, or it can be combined with gel precipitation and autoradiography to discriminate between antigens produced in orthopoxvirus infections (radioimmunoprecipitation, see below).

Hutchinson et al. (1977) developed a radioimmunoassay test for detecting species-specific orthopoxvirus antibodies in absorbed sera, which because of its sensitivity could be applied to sera obtained during field surveys.

ELISA method

Like the complement-fixation, immunofluorescence and radioimmunoassay tests, the ELISA (enzyme-linked immunosorbent assay) method provides a sensitive way of recognizing antigen–antibody reactions. It was developed rather too late to have been much used in research on smallpox and vaccination, but it constitutes a potentially useful field test for ecological studies of monkeypox, particularly if it can be used with a monkeypox-specific antigen or, in blocking tests, with suitable monoclonal antibodies.

Neutralization test

Neutralization of infectivity is the traditional discriminative test in animal virology, and is used to distinguish between different species of *Alphavirus* and *Flavivirus*, for example, or different strains of *Influenzavirus*. The antigens which evoke neutralizing antibodies after infection with orthopoxviruses, however, show a great deal of overlap (i.e., several epitopes are shared by all members of the genus), so that, as ordinarily performed, neutralization tests detect genus-specific rather than species-specific antibodies.

The neutralization of infectivity of orthopoxviruses can be carried out by testing virus–serum mixtures in experimental animals (rabbit skin: Parker, 1939; mouse brain: Bronson & Parker, 1941), or by looking for plaque or focus reduction in cultured cells (McNeill, 1965; Kitamura & Shinjo, 1972) or pock reduction on the chorioallantoic membrane (Keogh, 1936; McCarthy et al., 1958a). All species of *Orthopoxvirus* cross-react in neutralization tests, although titres are highest with the homologous virus (Downie & McCarthy, 1950; McNeill, 1968). In man, neutralizing antibody persists for many years after recovery from both smallpox and vaccination with vaccinia virus (McCarthy et al., 1958a,b; Downie & McCarthy, 1958).

Traditionally, neutralization tests have been carried out with suspensions of virions obtained by disrupting infected cells. Since such virions lack the envelope antigens found in naturally released virions (see Chapter 2), these neutralization tests do not measure all the antibodies that are important in protecting against infection or acting against circulating virions. Antibodies that neutralize the infectivity of enveloped virions can be assayed by the "anti-comet" test of Appleyard et al. (1971) (Plate 3.10). In essence, this test involves the use of a liquid overlay for cell monolayers infected with suitable concentrations of a strain of an orthopoxvirus, such as rabbitpox virus, that produces many enveloped virions. These migrate in the liquid overlay to produce comet-shaped areas of cell damage. Antibodies that neutralize the infectivity of envelope antigens, added after viral adsorption, prevent the formation of the "comets" but not the development of plaques. Antibodies to non-enveloped virions have no such effect, but prevent plaque production in orthodox neutralization tests, in which virus–serum mixtures are added to the monolayer.

Haemagglutination-inhibition (HI) test

All orthopoxviruses, but no other members of the family Poxviridae, produce a haemagglutinin which agglutinates cells from selected chickens. Because of its simplicity, the HI test has been widely used in serological surveys in man and in animals (e.g., for elucidating the ecology of monkeypox virus, see Chapter 29). The haemagglutinin appears early in the course of infection as one of several new components of the surface membrane of infected cells (Blackman & Bubel, 1972), where it may be recognized by haemadsorption tests (Driessen & Greenham, 1959).

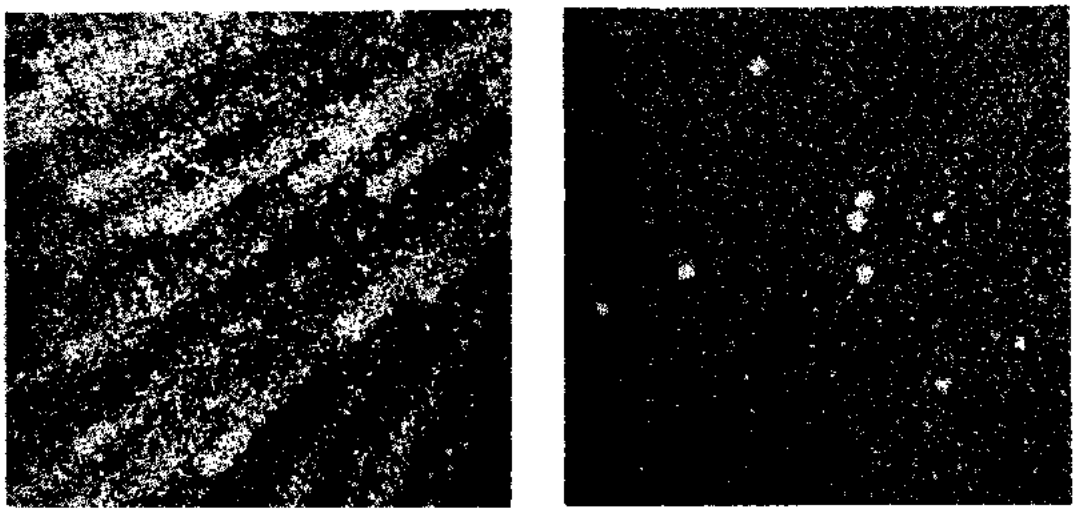


Plate 3.10. The "anti-comet" test. Strains of virus which produce substantial numbers of extracellular enveloped virions produce "comet tails" from the initial plaques when suitable dilutions are inoculated in monolayers with a liquid overlay medium (**A**). Addition to the overlay medium of antibody to viral envelopes or enveloped virions, or of antiserum from an animal that has been infected with vaccinia virus, prevents the production of the "comet tails" but not of the initial plaques (**B**). Antiserum to surface tubular elements or inactivated virions, although it neutralizes the infectivity of non-enveloped virions, does not inhibit "comet" formation. (From Appleyard et al., 1971.)

Haemadsorption tests are useful in confirming whether suspicious cytopathic effects in tissue culture are caused by an orthopoxvirus. The haemagglutinin also occurs as a component of the viral envelope (Payne & Norrby, 1976), but separately from infectious non-enveloped virions in extracts of infected cells. Haemagglutinins produced by different orthopoxviruses cross-react, although titres are usually higher with the homologous virus.

According to Downie and his colleagues (McCarthy et al., 1958b; Downie & McCarthy, 1958), antibodies with HI activity persist for varying periods after recovery from orthopoxvirus infection, usually for only a few months but somewhat longer than CF antibodies (see Fig. 3.6 and 3.7). Thus they were useful in determining whether recent infection with smallpox had occurred and were so used by Heiner et al. (1971a), but have limitations when used for epidemiological or ecological surveys aimed at determining the prevalence of orthopoxvirus infections. However, using a somewhat different protocol for the preparation of vaccinia haemagglutinin, Nakano (1985) found that HI antibodies were more persistent than previously thought. In tests on African subjects who had recovered from monkeypox, he found positive results in some individuals more than 4 years after recovery. Further, when sera from 600 Africans of all ages were tested for HI and neutralizing antibodies, more than 60% gave positive results by one or the other test. Most of these were positive by both tests but some gave positive results by HI but not by neutralization, and vice versa.

Non-specific inhibitors of orthopoxvirus haemagglutinin occur in some sera, especially if the specimens are old, have been improperly stored or were collected during autopsy. They can usually be removed from human sera without loss of specific antibody by treatment with potassium iodate (Espmark & Magnusson, 1964).

Some strains and mutants of orthopoxviruses fail to produce a haemagglutinin or to promote the production of HI antibodies (Cassel, 1957; Fenner, 1958). Experiments with these viruses, and other evidence, show that HI antibodies are unrelated to those involved in neutralization reactions, or to protection against infection, although the presence of HI antibodies is evidence that the antigens that do evoke the production of protective antibodies have been produced.

Precipitation tests

Much of the early work on the soluble antigens produced in orthopoxvirus-infected cells, involving both the time course of their

production (e.g., Appleyard & Westwood, 1964a) and comparisons between strains and mutants of orthopoxviruses (e.g., Gispen, 1955; Rondle & Dumbell, 1962), utilized simple gel-precipitation tests. With the use of absorbed sera, reactions can be detected which differentiate variola, monkeypox and vaccinia viruses (Gispen & Brand-Saathof, 1974; Esposito et al., 1977a). However, the sensitivity of simple gel-precipitation tests is low; they require highly potent sera and are not readily applicable to sera obtained from animals that have recovered from natural infections.

Gel precipitation used to be recommended as a method for rapid smallpox diagnosis, using vaccinia-immune sera and vesicle fluid or crust material as a source of antigen (World Health Organization, 1969a; see Chapter 2). It was widely used for rapid presumptive diagnosis in laboratories which lacked facilities for electron microscopic diagnosis (Rao, 1972; A.W. Downie, personal communication, 1981), but was rarely employed in WHO collaborating centres after electron microscopy by negative staining had been developed. Further, although it was almost always positive with fresh material (Noble et al., 1970), its efficiency was much lower (only about 70%) in material that had been dispatched from the field to a WHO collaborating centre (see Chapter 2, Table 2.10).

The sensitivity and discriminative power of gel precipitation were greatly enhanced by two modifications: (1) electrophoresis of the viral antigens or antigen–antibody complexes in SDS-polyacrylamide gels, and (2) radioisotopic labelling of the antigens. The radioimmunoprecipitation test was used by Ikuta et al. (1979) to demonstrate the presence of serologically related antigens among poxviruses of the same and different genera.

The Humoral Response in Relation to Pathogenesis

Until comparatively recently, the "immune response" was equated with the production of antibodies. It is now clear that cell-mediated immunity is of even greater importance than antibodies in the pathogenesis of many infectious diseases, and in every infected animal or human being with a normal immune system humoral and cellular immunity always operate simultaneously. It is convenient, however, to consider these two aspects of the immune response separately.

During infection with a virus as complex as an orthopoxvirus, antibodies of many different specificities are generated. Most of these are probably irrelevant, as far as the pathogenesis of poxvirus infections, recovery and protection are concerned. The relevant antibodies belong to three classes: (1) antibodies that neutralize viral infectivity, of which there are two subclasses, directed respectively against non-enveloped and enveloped virions (review: Boulter & Appleyard, 1973); (2) those that, with complement, lyse virus-infected cells (review: Sissons & Oldstone, 1980); and (3) antibodies that combine with circulating antigens to produce immune complexes, which might have been responsible for some of the "toxic" symptoms in smallpox.

It has long been believed that specific antibodies generated by the humoral immune response played important roles in both protection against orthopoxvirus infections and recovery from established infections. The protective effect of antibodies is most clearly demonstrated by passive immunization; their putative role in recovery was based mainly on temporal relationships observed during the course of established infections.

Passive immunity

Passive immunization, either natural, by the transmission of antibodies from mother to progeny, or by the inoculation of antisera, provides a means of examining the influence of antibodies on the disease process uncomplicated by cell-mediated immunity. The effect of passive immunization in protecting against infection with vaccinia virus was recognized as long ago as 1877 (Raynaud, 1877). The effectiveness and the limitations of passive immunization in generalized poxvirus infections are well illustrated in experiments on mousepox (Fig. 3.5). Active immunization with ectromelia virus (not illustrated) usually inhibited viral replication in the inoculated foot and always prevented generalization of the disease. Active immunization with vaccinia virus (Fig. 3.5B) had little effect on viral replication in the foot but greatly diminished generalization, although a transient rash sometimes occurred. The antibody titre rose and the relative titres against ectromelia and vaccinia haemagglutinins were reversed between 7 and 8 days after infection. Passive immunization was much less effective in modifying the course of the disease. Vaccinia-immune serum (Fig. 3.5D)

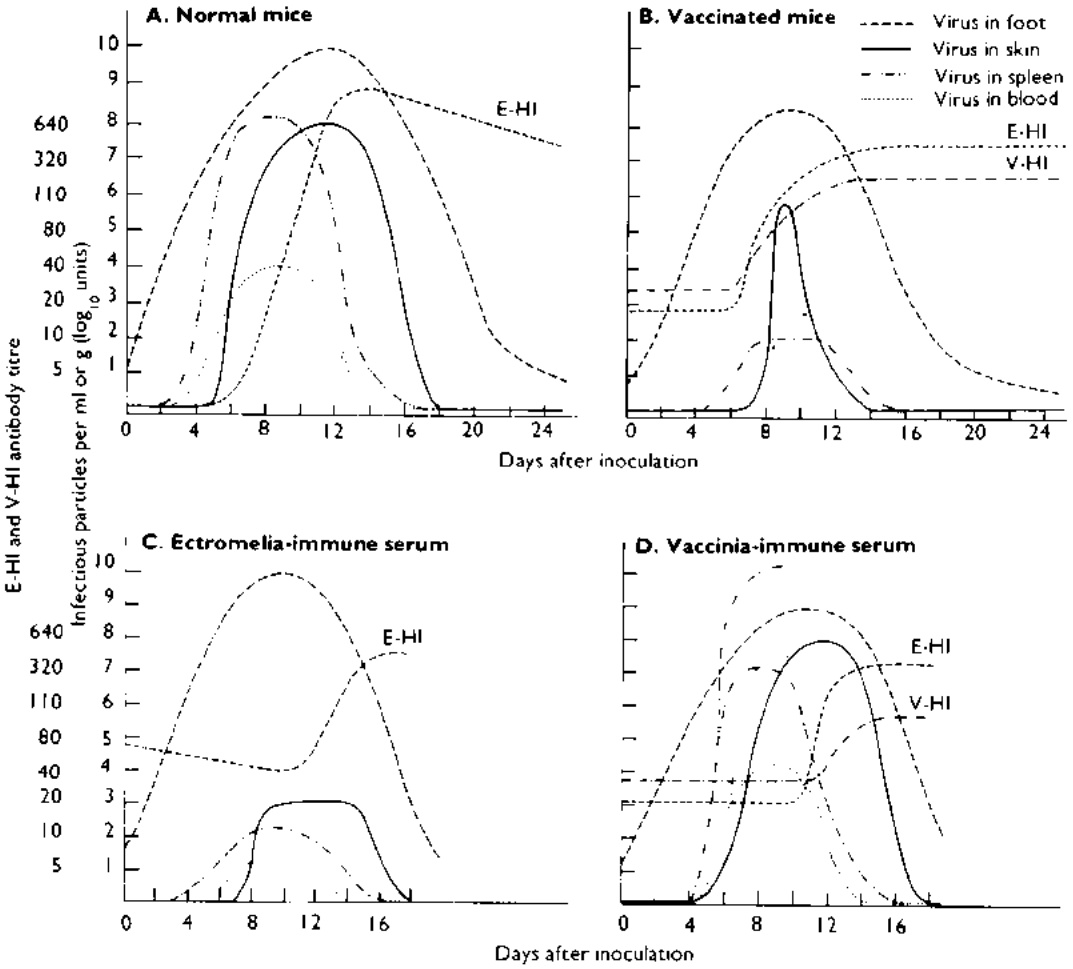


Fig. 3.5. The spread of ectromelia virus through the organs of mice, either unprotected (**A**), or protected by active immunization with vaccinia virus (**B**), or by passive immunization with ectromelia-immune serum (**C**) or vaccinia-immune serum (**D**) obtained from convalescent mice. E-HI and V-HI = haemagglutinin-inhibiting antibodies to ectromelia (E) and vaccinia (V) antigens. (From Fenner, 1949b.)

had almost no effect and several mice died with acute hepatitis at the same time as the controls. Ectromelia-immune serum (Fig. 3.5C) was more effective but did not influence viral replication in the inoculated foot, and a low level of replication in the spleen and skin was found in most animals. In passively immunized mice the antibody level rose about 2 days later than it did in the vaccinated mice.

These experiments illustrate two important features of passive immunization that are relevant to vaccination and smallpox in man. First, active immunization, whether heterologous (by vaccination) or homologous (after recovery from mousepox and, by analogy, from smallpox), provided much greater protection than the administration of preformed antibodies, even when the antibody titres in the passively immunized mice were higher than those in the actively immunized animals. The reason for the difference is that active immunization with infectious virus provokes the complete range of cell-mediated and humoral immune responses; passive immunization provides only the antibodies present in the convalescent animals from which the sera were obtained. Secondly, passive immunization with the homologous antibody provided much greater protection than did heterologous antibody, even though the sera cross-reacted extensively in neutralization tests. In relating these experiments to human vaccination and infection with variola virus it is important to realize that vaccinia and

variola viruses cross-react to a greater degree than do vaccinia and ectromelia viruses.

Experiments on passive immunization in rabbitpox (Boulter et al., 1961b) confirmed the protective value of potent homologous antiserum, which protected rabbits from death, even when treatment was delayed until overt disease had developed. Subsequent experiments (Boulter et al., 1971; see Table 3.5) showed that antisera produced after infection with live virus had a much greater protective effect than antiserum produced by immunization with inactivated virus, even when the neutralizing titre, measured by orthodox neutralization tests, was much lower.

Thus antibodies as such do have an effect on viral replication and spread in generalized poxvirus infections, although, as described below, cell-mediated immunity is probably more important. The influence of congenital passive immunization and the administration of antisera to smallpox cases or contacts is discussed in Chapter 1; the use of anti-vaccinial gamma-globulin in generalized vaccinia is dealt with in Chapter 7.

The antibody response during infections

In almost every kind of viral infection that has been studied, there is a relationship between the time at which circulating neutralizing antibodies first become detectable and the progressive decrease and eventual disappearance of virus in the blood and parenchymal tissues. However, the simultaneous activation of cell-mediated immunity and the possible earlier effects of interferon production (see below) make interpretation difficult.

Neutralizing antibodies and protective immunity

From the point of view of protection against natural infection, the antibody that neutralizes enveloped virions is theoretically more important than the antibody that neutralizes non-enveloped virions (review: Boulter & Appleyard, 1973). However, almost all reported studies of the role of neutralizing antibodies in the pathogenesis of poxvirus infections were carried out before the demonstration of the significance of enveloped virions, and assays of neutralizing antibodies have been performed with virus suspensions obtained by disrupting infected cells, and thus have measured antibody to non-enveloped virions. It is likely that relatively few virions circulate in this form during poxvirus infections; they are either cell-associated, in cells whose surface membranes may be altered by the incorporation of virus-specific antigens, some of which are similar to those found on the viral envelope, or they occur outside cells (in plasma or tissue fluids) as enveloped particles.

Antibody which specifically neutralizes enveloped virions can be detected by the "anti-comet" test (see Plate 3.10). The differences between neutralizing antibodies to enveloped and non-enveloped virions are particularly important in relation to efforts to produce inactivated vaccines for protection against smallpox (see below). The relevant features of the experiments by Boulter, Appleyard and their colleagues (Appleyard et al., 1971; Boulter et al., 1971; Turner & Squires, 1971) and later experiments by Payne (1980) can be summarized as follows:

(1) Sera of rabbits which had recovered from infection with rabbitpox virus contained antibodies that neutralized enveloped virions; sera from rabbits inoculated with inactivated virions lacked such antibodies.

(2) Sera from both groups of rabbits neutralized non-enveloped virions.

(3) Cross-absorption of the two types of sera with concentrated enveloped or non-enveloped virions selectively removed neutralizing antibodies of the appropriate specificity.

(4) Antibody to isolated envelopes was able to neutralize the infectivity of enveloped virions and to protect mice against the spread of infection.

(5) Rabbits immunized with inactivated rabbitpox virus (i.e., with inactivated non-enveloped virions) had high levels of neutralizing antibodies to non-enveloped and none to enveloped virions, but showed only partial immunity on challenge inoculation, whereas rabbits immunized with enveloped virions were fully protected.

Antibody-mediated complement-dependent lysis

Oldstone and his collaborators (reviews: Oldstone & Lampert, 1979; Sissons & Oldstone, 1980) have shown that antibodies can exert a number of significant effects on virus-infected cells. In conjunction with complement or cytotoxic lymphocytes, IgG antibody can mediate the destruction of virus-infected cells. In experiments with vaccinia in humans,

Perrin et al. (1977) suggested that lysis of virus-infected cells was more likely to be due to non-specific "killer" lymphocytes (NK cells) acting in the presence of antibody to viral antigens located in the cell membrane than to specifically sensitized cytotoxic lymphocytes.

Immune complexes as a cause of toxaemia

Soluble orthopoxvirus antigens and immune complexes could be readily demonstrated in the plasma of severe cases of smallpox (Downie et al., 1953). It is possible that these immune complexes played a part in the production of the toxaemia that was so characteristic of variola major.

Methods for Measuring Cell-Mediated Immunity

Nature of the cells involved

Although observers had long been concerned with the frequent lack of correlation between circulating antibodies and recovery from infections, "cellular immunity", invoked in such situations to explain recovery from disease, had no precise meaning until the complex immunospecific responses of T cells were recognized during the 1970s, distinct and independent of the antibody-producing B cells. The T-cell responses, other than those involved in modulation of the humoral response (see Fig. 3.4), constitute cell-mediated immunity. The mechanisms by which T lymphocytes exercise antiviral functions are complex; they may involve both the direct effects of T cells on cells with virus-modified surface membranes and the effects of their secreted products, which are called lymphokines and include, among others, gamma-interferon.

The delayed hypersensitivity reaction

The classical method of measuring cell-mediated immune responses is the skin test for delayed hypersensitivity, an expression used to contrast the time course and nature of the reaction with that of "immediate" hypersensitivity, which comes on within minutes of exposure to the relevant antigen and is mediated by IgE (Gell et al., 1975). It is a complex reaction involving three components: (1) an initial one in which antigen-sensitive T cells are sensitized, a procedure that may require the prior processing of antigens in macrophages; (2) a further component, consisting of antigen recognition and the proliferative response of T cells, with release of lymphokines; and finally (3) an inflammatory response which is amplified by chemotactic factors. Delayed hypersensitivity can be passively transferred by suspensions of lymphoid cells, but not by antiserum. Two subclasses of T cell may be involved in delayed hypersensitivity reactions (Fig. 3.4): (1) cytotoxic T cells (Tc) are evoked by viral infection and have cytotoxic activity, reacting specifically with virus-induced antigens on cell membranes; (2) delayed hypersensitivity T cells (Td) are evoked by antigen presented in a non-multiplying form, such as inactivated vaccines, as well as during viral infections; these T cells are not cytotoxic (Ada et al., 1981).

Delayed hypersensitivity is recognized by the accelerated response to inoculation of the antigen(s) into the skin; its development during vaccine inoculation of man was recognized by Jenner (1798) and has been repeatedly demonstrated since then (e.g., Pincus & Flick, 1963). It was commonly used as a method of assessing immunity to smallpox, but its reliability for this purpose depended on which kind of T cells produced the reaction. If they were cytotoxic T cells produced by prior infection with active virus, delayed hypersensitivity was a good index of resistance. If they were the kind of T cell (Td) provoked by a non-multiplying antigen, which lacked cytotoxic capacity, there was usually no correlation between delayed hypersensitivity and resistance—i.e., delayed hypersensitivity is an indicator of resistance only when it is an indicator of the presence of cytotoxic T cells (Ada et al., 1981).

In vitro *techniques for analysing T-cell function*

There is no satisfactory *in vitro* assay of delayed hypersensitivity; the reaction involved is a particular kind of inflammatory response which must be tested in intact animals. However, in experimental systems there is a good assay for cytotoxic T cells. A known number of ^{51}Cr-labelled, virus-infected target cells are cultured together with varying numbers of lymphocytes obtained from the spleen or lymph nodes. The release of the radioactive label is an index of cytotoxic T-cell activity; proof that it is due to T cells is provided by the absence of lysis if the

lymphocyte preparation is treated with anti-theta serum and complement.

In vitro experiments with cells infected with ectromelia virus (Ada et al., 1976; Jackson et al., 1976) and with vaccinia virus (Koszinowski & Ertl, 1976) showed that some of the cell-surface changes relevant to T-cell-mediated lysis occurred before viral DNA replication had begun—i.e., they were "early" synthetic functions coded for by the input DNA.

The mechanism of cytotoxic T-cell lysis was shown by Zinkernagel & Althage (1977) to be a direct interaction between the appropriate T cells and cells infected with vaccinia virus. Recognition by T cells depended on the presence on the membranes of infected cells of both virus-specified antigens and the appropriate major histocompatibility gene products. The early lytic effect ensures that cells are lysed before progeny virions are assembled and thus accounts for the efficiency of cell-mediated immunity in the control of established infections with orthopoxviruses (see below).

Cell-Mediated Immunity in Relation to Pathogenesis

There is even more need to make use of model systems in laboratory animals to elucidate the role of various components of the immune response in smallpox than in studies of the spread of infection during the incubation period. Mice are particularly suitable, since so many genetically defined mouse lines are available. Mousepox, which proved so useful for studying other aspects of pathogenesis, is the system most likely to provide clues as to the relative importance of humoral and cell-mediated immunity in smallpox, and has been extensively exploited for this purpose (Blanden, 1970, 1971a,b; reviews: Blanden, 1974; Cole & Blanden, 1982).

Experiments with mousepox

Mechanisms controlling viral growth in the major visceral target organs (liver and spleen) become operative 4–6 days after primary infection by the natural route, which in the experimental studies was simulated by subcutaneous inoculation into the footpad. Cell-mediated immune responses occur soon after infection: virus-specific cytotoxic T cells are detectable 4 days after infection and reach peak levels in the spleen 1–2 days later, while delayed hypersensitivity is detectable by the footpad test 5–6 days after infection. In contrast, significant neutralizing antibody is not detectable in the circulation until the 8th day.

Mice pretreated with anti-thymocyte serum, which acts specifically on T lymphocytes, die from otherwise sublethal doses of virus, because of uncontrolled viral growth in target organs. Such mice have impaired cell-mediated responses but their neutralizing antibody levels are normal, interferon levels in the spleen are elevated, and the innate resistance in target organs is unchanged.

Very large doses of interferon or immune serum transferred to previously infected recipients are relatively ineffective against the established infection in target organs, although high levels of interferon and high antibody titres can be demonstrated in the sera of the recipients. On the other hand, immune spleen cells harvested 6 days after active immunization of the donor transfer specific and highly efficient antiviral mechanisms which rapidly eliminate infection from the target organs of the recipients, in whose serum neither antibody nor interferon is detectable. The active cells in the immune population can be identified as cytotoxic T cells. Mononuclear phagocytes of immune T-cell recipients, labelled with tritiated thymidine before T-cell transfer, appear in foci of infection in the liver after T-cell transfer, and prior irradiation of immune T-cell recipients in a regimen designed to reduce blood monocyte levels significantly reduces the antiviral efficiency of the transferred cells.

These findings support the idea that blood-borne cytotoxic T cells with immunological specificity for virus-induced antigenic changes in infected cell surface membranes enter infectious foci and retard viral spread by lysing infected cells before the maturation and assembly of progeny virions. This T-cell activity attracts blood monocytes which contribute to the elimination of infection by phagocytosis and intracellular destruction of virus. Macrophage activation and locally produced interferon may increase the efficiency of virus control and elimination, but are less important than T cells.

Recognition of the importance of cytotoxic T cells in controlling the replication of ectromelia virus in foci of infection does not mean that humoral antibodies do not also play a role in pathogenesis. Indeed, the early

experiments of Fenner (see Fig. 3.5) with convalescent antiserum from ectromelia-immune animals showed that antisera do have an effect on the progression of infection, probably in controlling the viraemia.

The Immune Response in Smallpox

Because it is so easy to obtain serum, because many serological tests for antibodies are simple to perform, and because the development of knowledge about cell-mediated immunity is relatively recent, studies of the immune response in smallpox and after vaccination are dominated by reports on the humoral component of the immune response and very deficient in observations on cell-mediated immunity.

Antibody production in cases of smallpox

The most comprehensive studies on the serological responses to smallpox are those reported by Downie and his colleagues in 1958 and 1969. Working with variola major patients in Madras, India, Downie et al. (1969a,b) examined the sera of 151 patients with ordinary-type and modified-type smallpox, 37 patients with early haemorrhagic-type smallpox and 40 patients with late haemorrhagic-type smallpox.

In non-haemorrhagic smallpox haemagglutinin-inhibiting (HI) and neutralizing antibodies showed rising titres from the 6th day of illness (i.e., approximately 18 days after infection) and most patients developed antibodies demonstrable by gel precipitation or by complement fixation (CF) some 2 days later. Most of the patients studied were adults who had scars attributed to childhood vaccination; the antibody response usually occurred a few days later in unvaccinated than in vaccinated patients.

Most of the patients with haemorrhagic-type smallpox were adults with old vaccination scars (Rao, 1972). Their antibody responses were much lower, and occurred later, than those of patients suffering from ordinary-type or modified-type smallpox. Only 5 patients, all with late haemorrhagic-type smallpox, developed antibody that reacted in the precipitation test; 4 of these patients and 2 others were the only ones with CF antibody. Tests for HI antibody, on the other hand, were almost always positive and the titres were comparable to those found in non-haemorrhagic smallpox. The titres of neutralizing antibodies were much lower than those in non-haemorrhagic smallpox and the reaction was often still negative when the patient died. Cases of haemorrhagic-type smallpox, but not other types, always had high and sustained viraemia and antigenaemia (see Fig. 3.2).

Another important aspect of the humoral response was the persistence of antibodies after recovery from smallpox, as detected by different tests. Downie & McCarthy (1958) provide relevant data on some of the sera from 32 British cases of variola major (of whom 25 survived) and 19 cases of variola minor. The results (Fig. 3.6), expressed on several time frames and on a logarithmic time scale, showed that the levels of neutralizing and HI antibodies rose on about the 6th day of illness and the level of CF antibodies about 2 days later. Neutralizing antibody titres usually persisted for several years, HI titres usually fell to low levels by the 5th year after infection, and CF antibody titres rarely persisted for as long as 1 year.

Cell-mediated immunity in smallpox

Understanding of the importance of cell-mediated immunity in the recovery process in poxvirus infections came too recently for appropriate studies to have been conducted in cases of smallpox, although it would have been of considerable interest to see whether the T-cell responses were defective in flat-type and haemorrhagic-type smallpox. The extent of the rash precluded studies of delayed hypersensitivity by skin tests. The only report on cellular immunity in smallpox is that of Jackson et al. (1977), who determined the proportion of T and B cells in the peripheral blood of 17 smallpox patients in Bangladesh, at times varying between 3 and 21 days from the onset of illness. The T-cell counts were consistently lower in smallpox patients than in the controls; in 2 out of 4 fatal cases the B-cell counts were lower than in any of the controls. The 2 patients who had the highest null cell counts (lymphocytes not identified as either T or B cells) died, while 5 patients with consistently low null cell counts survived. Since no effort was made to determine the nature of the T cells studied, this result can only be regarded as preliminary. If it were possible to carry them out, studies on patients with human monkeypox would provide the only opportunity left to extend these investigations.

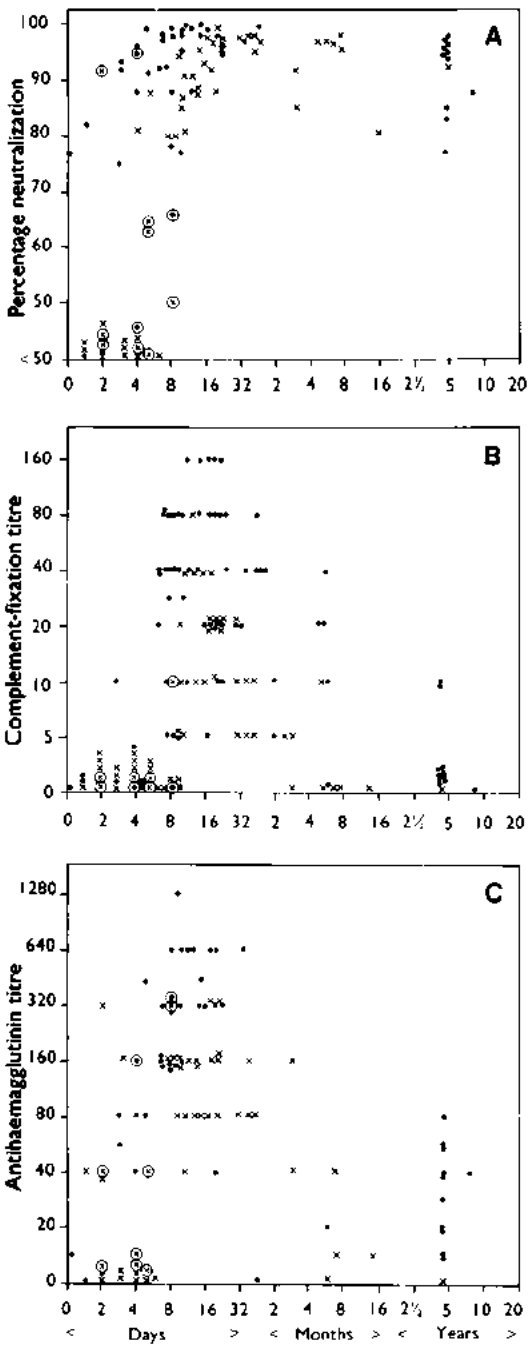


Fig. 3.6. Antibody production and persistence in cases of non-haemorrhagic smallpox (variola major and variola minor, not differentiated), as determined by various tests. **A**: Neutralization of variola virus pock production on the chorioallantoic membrane; **B**: Complement fixation with vaccinial antigens; **C**: Inhibition of haemagglutination by vaccinia haemagglutinin. Note that the abscissa has several time scales, all logarithmic, and that day zero corresponds to the onset of illness—i.e., about 12 days after infection. ● = vaccinated; × = unvaccinated; ◉, ⊗ = fatal cases. (From Downie & McCarthy, 1958.)

The Immune Response after Vaccination

There have been numerous studies of the immune response after vaccination, in both human subjects and laboratory animals, especially rabbits. Most have been concerned only with humoral antibodies and, when neutralizing antibodies were assayed, only with tests involving non-enveloped virions.

Antibody production after vaccination

The results obtained by Downie and his colleagues in vaccinated and revaccinated human subjects (McCarthy et al., 1958b) provide comparability with the antibody responses in smallpox just described. Following primary vaccination, no antibody was detected up to the 10th day, after which neutralizing and HI antibodies were present in the majority of individuals and CF antibodies in less than half (Fig. 3.7). Neutralizing antibodies were clearly much the most persistent, sometimes being demonstrable for more than 20 years after primary vaccination. HI antibody was less persistent, and its persistence varied more markedly from subject to subject. CF antibody was not found more than 6 months after primary vaccination. In revaccinated individuals (several of whom possessed neutralizing antibodies before revaccination), the antibody titres tended to be higher, and when a response occurred, it began earlier, often within 7 days. In several revaccinated individuals CF and HI antibodies failed to appear even when there was a substantial rise in neutralizing antibody. It was noteworthy that only about half the revaccinated subjects who showed an "early" or "immediate" type of vaccination response developed neutralizing antibody.

When these results are compared with those recorded in Fig. 3.6 for non-haemorrhagic smallpox, it is clear that, calculated from the time of infection rather than the onset of disease, antibodies appeared more quickly after vaccination than in an attack of smallpox. The disparity was even greater in revaccinated subjects. This result, not unexpected in view of the much shorter incubation period and more rapidly progressive disease process in vaccinia (see Fig. 3.1 and Chapter 1, Fig. 1.3), explains why primary vaccination, given early after exposure, often modified and sometimes aborted an overt attack of smallpox. The appearance of neutralizing antibodies after vaccination with live virus is an

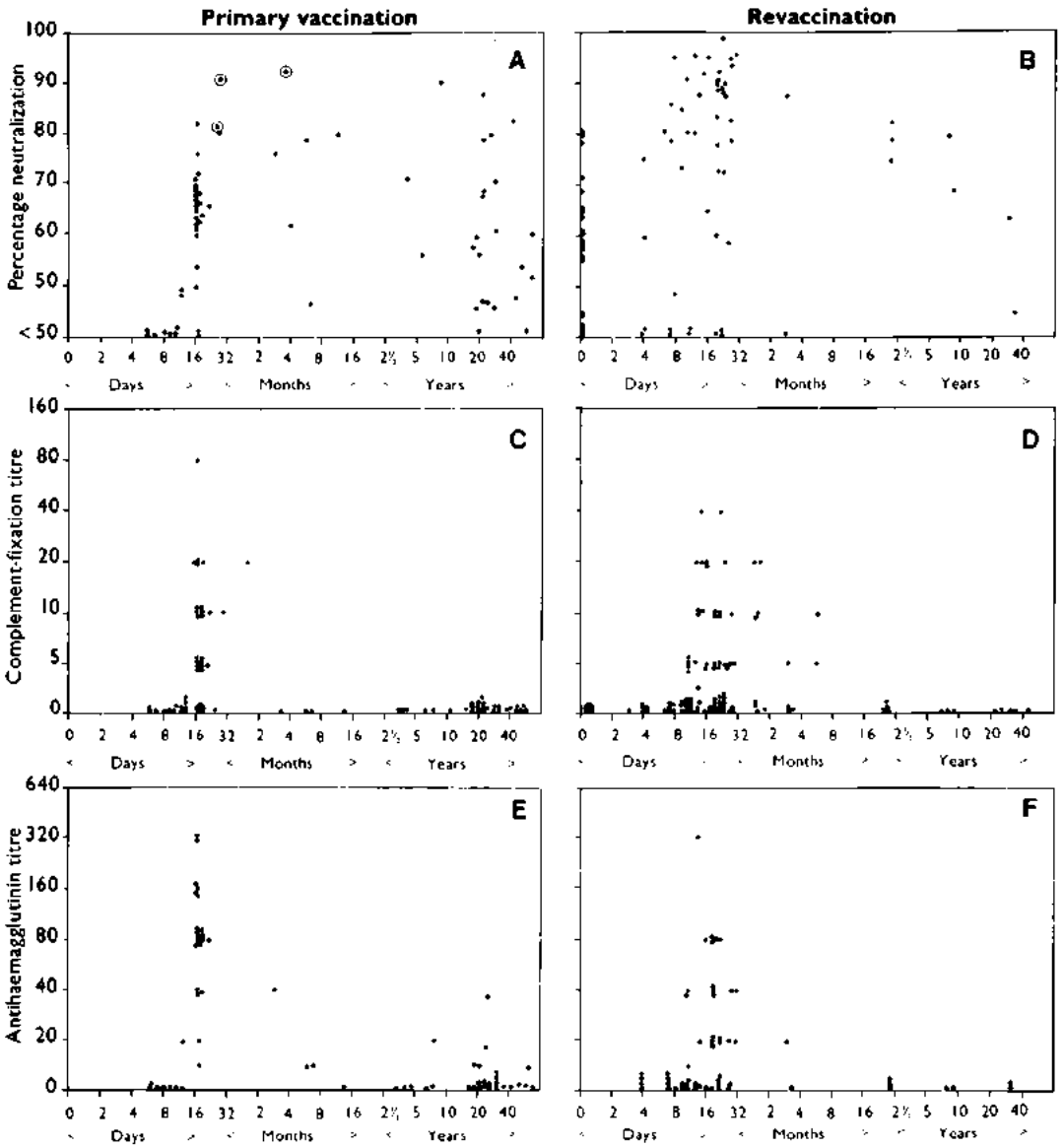


Fig. 3.7. Antibody production and persistence after primary vaccination (panel on left: **A**, **C**, **E**) and revaccination (panel on right: **B**, **D**, **F**), as determined by various tests. **A** and **B**: Neutralization of variola virus pock production on the chorioallantoic membrane; **C** and **D**: Complement fixation with vaccinial antigens; **E** and **F**: Haemagglutination inhibition of vaccinia haemagglutinin. Note that the abscissa has several time scales, all logarithmic, and that day zero corresponds to the day of infection with vaccinia virus. Circled dots in **A** represent cases of generalized vaccinia. (From McCarthy et al., 1958b.)

index of an active immune response which would include the development of antibodies to all viral antigens, as well as increased cell-mediated immunity. The accelerated immune response in revaccination (within a week, compared with over 10 days in primary vaccination) was of considerable importance in protecting persons by vaccination after exposure to smallpox.

Cell-mediated immunity after vaccination

Pincus & Flick (1963) demonstrated that delayed hypersensitivity, which is one index of cell-mediated immunity, developed rapidly after vaccination; they suggested that it played an important role in the pathogenesis of vaccinial lesions, both after primary vaccination and after revaccination. By vaccinating children twice, at intervals of 2 days,

they showed that the incubation periods for the 2nd vaccination, with regard to both papule and vesicle, were greatly shortened.

A delayed hypersensitivity response can be elicited in vaccinated subjects by either killed or active vaccine (Benenson, 1950), so that an "immediate" reaction to revaccination (reaching its maximum within 72 hours) does not necessarily mean that the subject's immunity has been boosted by reinfection. Nevertheless, it indicates that he possesses some residual allergy. If a potent live vaccine is used, with a satisfactory technique, this may be the only reaction seen in highly immune subjects. In those in whom immunity has waned somewhat this allergic response is followed by an enlarging area of erythema, often with vesiculation in the centre, which becomes maximal earlier than in a primary vaccination. The absence of such erythema by the 3rd or 4th day after primary vaccination is indicative of a deficient cell-mediated immune response and such patients may suffer from progressive vaccinia (see below).

Immunological deficiency states in man

The effects of immunological deficiency states in human subjects who had been vaccinated with vaccinia virus provides the best available information on the relative importance of cell-mediated and humoral responses in determining recovery in orthopoxvirus infections in man. Fulginiti et al. (1968) described a number of cases of progressive vaccinia (vaccinia necrosum) in such infants and children, and Kempe (1980) has summarized his extensive experience with these conditions, in relation to vaccination. In children with immunological defects in cell-mediated immunity, vaccinia virus replicated without restriction, resulting in a continually progressive primary lesion (see Chapter 7, Plate 7.8B), persistent viraemia and widespread secondary viral infection of many organs, including the skin. This response was particularly severe in patients with thymic alymphoplasia. In patients with thymic dysplasia and partially or completely intact immunoglobulin-synthesizing capacity (Nezelof's syndrome) the progression of the primary disease was sometimes slower and less persistent, but a fatal outcome was usual (Kumar et al., 1977).

Fig. 3.8 sets out various kinds of immunological defect schematically and suggests the kinds of response that occurred when such individuals were vaccinated. Cell-mediated immunity was clearly of major importance in controlling vaccinial infection, since individuals with defects in cell-mediated immunity but intact antibody production (Categories 3 and 5, Fig. 3.8) suffered from progressive vaccinia, while those with defects in antibody production but a satisfactory capacity to mount a cell-mediated immune response (Category 4) usually reacted normally to vaccination. Freed et al. (1972) suggested that in some circumstances, especially when the immunological defect was acquired (Category 6), the administration of vaccinia-immune globulin (VIG) would allow cell-mediated immunity to recover sufficiently to control the vaccinial infection. Also, in some cases of Bruton's syndrome a partially deficient cell-mediated immune mechanism might have been "overwhelmed", but could be restored to effectiveness by the administration of vaccinia-immune globulin.

Delayed hypersensitivity reactions could never be evoked in patients with progressive vaccinia, nor could the peripheral blood lymphocytes of such patients be stimulated to mitosis by exposure to inactivated vaccinia virus (Fulginiti et al., 1968). Although neutralizing antibody was sometimes present in the serum, its presence did not prevent the development of progressive vaccinia if cell-mediated immunity was defective (Hansson et al., 1966). Kempe (1980) records having seen 15 boys with very low levels of gammaglobulin, who had been routinely vaccinated in infancy without complications. All had histories of "enormous and hyperactive" delayed hypersensitivity responses to vaccinial antigens.

Cells Involved in Immunological Memory

By far the most important aspect of vaccination against smallpox was the fact that the vaccinated individual was primed, so that he responded more quickly and effectively than an unvaccinated person to infection with the antigenically related variola virus. Orthopoxvirus-specific T-cell and B-cell memory can be envisaged as comprising previously induced lymphocytes, of both T and B classes and all subclasses, which persist as non-functioning long-lived cells in lymphoid tissues and the recirculating pool of lymphocytes. In the spleens of mice infected with ectromelia virus, the appearance of memory T

Immunological condition	Immunological status	Response to vaccination
1. Normal, vaccinated	(+)CMI+ ; (+)Ab+	CMI+ ; Ab+ : no change
2. Normal, unvaccinated	(+)CMI− ; (+)Ab−	CMI+ ; Ab+ : primary vaccination
3. Thymic dysplasia	(−)CMI− ; (+)Ab−	CMI− ; Ab+ : progressive vaccinia ↘ VIG ↘ CMI− ; Ab+ : progressive vaccinia
4. Bruton's syndrome	(+)CMI− ; (−)Ab−	CMI+ ; Ab− : primary immunization or CMI− ;Ab−(CMI "overwhelmed"): progressive vaccinia ↘ VIG ↘ CMI+ ; Ab+ : CMI restored—recovery
5. Swiss syndrome	(−)CMI− ; (−)Ab−	CMI− ; Ab− : progressive vaccinia ↘ VIG ↘ CMI− ; Ab+ : progressive vaccinia
6. Acquired deficiencies (e.g., lymphoma)	(−)CMI− ; (−)Ab−	CMI− ; Ab− : progressive vaccinia ↘ VIG ↘ CMI+ ; Ab+ : CMI restored—recovery

Fig. 3.8. The response of normal individuals and individuals with immunological defects to vaccination. Progressive vaccinia is associated with a defective cell-mediated immune response, but under some circumstances vaccinia-immune globulin can be useful (see text). CMI = cell-mediated immunity; Ab = antibody production; VIG = vaccinia-immune globulin; (+) or (−) = potential for CMI or Ab response; + or − = presence or absence of appropriate response. (Based on Freed et al., 1972.)

cells coincides with the disappearance of primary cytotoxic T-cell activity, which falls off rapidly after viral clearance (Gardner & Blanden, 1976). After mediating viral clearance, primary cytotoxic T cells apparently dedifferentiate and lose their lytic capacity, and on restimulation with antigen, which occurs on reinfection, the sequence is reversed. In addition, in the primed individual there are memory helper T cells whose functional activity can only be expressed in the presence of antigen, when they elaborate factors that amplify the functions of B cells and of other subclasses of precommitted T cells.

The role of memory T cells in persisting immunity to orthopoxvirus infections increases in importance as the interval between primary and secondary infections increases, since as long as pre-existing antibody of the correct specificity persists this probably aborts infection at the portal of entry. Later, the ability to mount a rapid cell-mediated immune response would assist greatly in limiting the growth of virus and extension of the infectious foci.

REDUCING THE RISKS OF VACCINATION

Vaccination was introduced and its efficacy established by the most relevant and stringent criterion, its ability to provide protection against smallpox, almost a century before immunological techniques were developed.

After smallpox had been eliminated from Europe and North America in the 1950s, the public in these countries did not readily tolerate the degree of illness—not to say the occasional episodes of severe illness or even deaths, which occurred, for example, in eczematous children and those with an immunological deficiency—that were associated with standard smallpox vaccination. Two ways were sought to provide immunization against smallpox without the attendant risks of severe disease: the use of attenuated strains of vaccinia virus and the use of inactivated vaccines.

The assessment of the efficacy of either of these kinds of vaccine presented obvious problems, since the real criterion for their value was the ability of the vaccine to protect against smallpox and the durability of this protection. On ethical and practical grounds it was not possible to test new vaccines in this way, so two other criteria were used in their assessment: the neutralizing antibody response and protection against challenge inoculation of standard vaccine, supplemented, in experiments with animals, by protection against an otherwise lethal challenge with a suitable orthopoxvirus.

By all three tests the standard vaccine strains provided excellent protection against smallpox. The situation was less clear-cut with attenuated vaccinia virus vaccines, which are discussed at some length in Chapter 11. There appeared to be serious deficiencies in protection when inactivated vaccines were used, the reasons for which are outlined below.

Inactivated Virus Vaccines

The production of an inactivated smallpox vaccine seemed a feasible procedure, since it was relatively easy to grow and purify large amounts of vaccinia virus. Many methods of inactivation were tested (Kaplan, 1969; Turner et al., 1970), including heat, formaldehyde, ultraviolet irradiation, photodynamic inactivation and gamma irradiation.

As described in Chapter 2, there are major antigenic differences between the surface antigens of enveloped and non-enveloped virions, both of which are infectious. Smallpox vaccine, however it was grown, was prepared in such a way that it consisted predominantly of non-enveloped virions. The infection provoked by vaccination with live vaccine led to the development of both enveloped and non-enveloped virions and the full range of humoral and cellular immune responses. In contrast, inactivated virions failed to provoke a humoral response to the envelope antigens (Appleyard et al., 1971; Turner & Squires, 1971; Payne, 1980), nor did they stimulate the production of cytotoxic T cells (Ada et al., 1981).

Experiments with inactivated vaccines highlighted the lack of correlation between levels of neutralizing antibody (measured against non-enveloped virions) and protection. Thus immunization of rabbits with a vaccinia virus "soluble antigen" gave a good antibody response and protection against intradermal challenge with vaccinia virus, but resistance to the more virulent rabbitpox virus was less than that induced by live vaccinia virus, despite the fact that the live virus induced much less antibody (Appleyard & Westwood, 1964b). Rabbits immunized by multiple intradermal injections followed by 6 intravenous injections of heat-inactivated vaccinia virus developed high titres of neutralizing antibody, but even after this intensive course there was only partial protection against challenge infection with rabbitpox virus (a virulent strain of vaccinia virus) (Madeley, 1968). Similarly, rabbits immunized with large doses of vaccinia virus inactivated by formaldehyde or ultraviolet irradiation developed extremely high titres of neutralizing antibody (tested against non-enveloped virions), but they remained susceptible to generalized rabbitpox infection, although protected from death (Boulter et al., 1971). The importance of antibody against enveloped virions was most clearly demonstrated by experiments on the passive transfer of resistance with antiserum (Table 3.5). Antisera against inactivated virus, with very high levels of neutralizing antibody to non-enveloped but none to enveloped virions, provided much weaker protection against challenge infection than apparently much lower titres of antibody induced by infectious virus, which, however, contained both kinds of neutralizing antibody.

More recently, Olsen et al. (1977) reported that an inactivated vaccine prepared by mechanically disrupting monkeypox virions protected monkeys against disease when they were challenged with active monkeypox virus, although it did not prevent infection. There were two significant features in these experiments. First, immunization was carried out with the homologous virus. The second—

Table 3.5. Comparison of the protective activity of three types of antiserum administered passively to rabbits before challenge infection with rabbitpox virus[a]

Antiserum			Response to challenge	
Against	Source	Neutralization titre	Fever	Death
Inactivated vaccinia virus	Horse	800 000[b]	12/12	5/12
	Sheep	500 000[b]	5/5	4/5
Live vaccinia virus	Sheep	150 000[c]	4/5	0/5
	Rabbit	19 000[c]	8/10	0/10
Live rabbitpox virus	Rabbit	32 000[c]	0/5	0/5
None	—	—	18/18	15/18

[a] From Boulter et al. (1971).
[b] Measured against non-enveloped virions; no neutralizing antibodies to enveloped virions.
[c] Measured against non-enveloped virions; neutralizing antibodies to enveloped virions also present.

and more important—feature was that, although the inactivated preparation had no haemagglutinating capacity, it elicited the production of haemagglutinin-inhibiting as well as neutralizing antibodies, demonstrating that the method of inactivation left at least some of the envelope antigens intact.

It also appears that inactivated virus provokes a rather different kind of cell-mediated immune response from that found after infection, eliciting delayed hypersensitivity T cells but not cytotoxic T cells (Ada et al., 1981), perhaps because the surface antigens involved in infected cells are not produced, or because the mode of inoculation results in too localized and immobile an antigenic mass. Indeed, the delayed hypersensitivity reaction itself was deficient in rabbits immunized with inactivated vaccine. For example, Turner et al. (1970) and Turner & Squires (1971) found that inactivated vaccines did not produce an obvious delayed hypersensitivity response, although the animals responded more rapidly than did the controls to challenge inoculation with live virus.

Thus, inactivated vaccines suffered from two defects: they failed to elicit antibodies that neutralized enveloped virions and they failed to provoke the production of cytotoxic T cells. In addition, the adverse effects of inactivated measles virus vaccines, which became evident in the mid-1960s (Fulginiti et al., 1967), made public health authorities reluctant to consider another inactivated virus vaccine when there was already a successful live virus vaccine available. Nevertheless, in an effort to reduce the incidence and severity of postvaccinial encephalitis, formalin-inactivated vaccine ("vaccinia-antigen") was used in the German Democratic Republic and the Federal Republic of Germany during the late 1960s (see Chapter 11) for a "priming" vaccination, followed by vaccination with standard vaccine. Subsequently, Marennikova & Macevič (1975) showed that pre-immunization of rabbits with vaccine inactivated by ^{60}Co gamma-irradiation greatly enhanced their response to vaccination with active vaccine given 7–60 days later, both in the titre of antibody produced and in its rate of production. Pre-immunization reduced the incidence of viraemia in the rabbits 4–5 days after vaccination with live virus. Preliminary human trials on the use of this preparation as a priming antigen were carried out in eastern Europe in 1977 (see Chapter 11).

NON-SPECIFIC MECHANISMS INVOLVED IN HOST DEFENCE

The efficacy of vaccination and the increased susceptibility of individuals with certain immunological defects illustrate clearly the great importance of the immune response in orthopoxvirus infections. There are nevertheless a number of defence mechanisms against viral infections whose activity is not specific in an immunological sense. Most of these are ill-understood and it is difficult to evaluate their importance in orthopoxvirus infections.

Body Temperature

As outlined in Chapter 2, determination of the ceiling temperature of viral replication is a useful laboratory method of distinguishing between certain orthopoxviruses and between variola major and certain strains of variola minor virus. In animal models, body tempera-

ture has a dramatic effect on the severity of the leporipoxvirus disease, myxomatosis (Marshall, 1959), and mice housed at 2 °C are about 100 times more susceptible to mousepox than those maintained at 20 °C (Roberts, 1964).

There is no evidence that raised body temperature affected the progress of variola major; severe cases (flat-type and haemorrhagic-type smallpox) were often associated with higher temperatures than those found in ordinary-type smallpox. However, Dumbell & Wells (1982), comparing variola major and alastrim (variola minor) viruses, found that many fewer virions of alastrim (variola minor) virus (which had the lower ceiling temperature) than of variola major virus were released from infected cells when the temperature was raised. The decreased dissemination of virus could act in concert with developing immunity to reduce the severity of variola minor.

Nutrition

Almost any severe nutritional deficiency will interfere with the activity of phagocytes, and the integrity of the skin and mucous membranes is impaired in many types of nutritional deficiency (review: Scrimshaw et al., 1968). Immunoglobulin levels, antibody responses and the numbers of circulating B cells are generally normal in cases of moderate to severe malnutrition, but cell-mediated immunity is consistently impaired, whether measured by cutaneous delayed hypersensitivity tests or by the numbers of circulating T cells (Chandra, 1979). The number of null cells—i.e., cells without the surface characteristics of T or B cells, which suppress the activity of other lymphocytes—was relatively increased in cases of malnutrition. It will be recalled that the proportion of such cells was substantially increased in patients with smallpox and that there seemed to be a correlation between the height of the null cell count and the prognosis (Jackson et al., 1977).

Little information is available about the effect of malnutrition on smallpox, although it seems clear that its effects were not as dramatic as those seen in measles in young children in many African countries. The mortality of variola major in unvaccinated infants was so high that it was difficult to determine whether nutritional deficiency was important. However WHO epidemiologists working in Ethiopia and Somalia noticed that

1961

Plate 3.11. Rijk Gispen (b.1910). Formerly Director of the National Institute of Public Health at Bilthoven, Netherlands. Gispen was an important contributor to the immunology of orthopoxvirus infections from the 1950s to the 1970s. He was the first to develop methods of differentiating between antibodies due to infection with monkeypox, variola and vaccinia viruses.

variola minor was much more severe in malnourished than in well-nourished infants.

The occurrence of blindness after smallpox is said usually to have been associated with secondary bacterial infection or nutritional deficiencies.

Age

Among unvaccinated persons, smallpox produced its highest mortality in the very young and the aged, and its lowest in the age group 5–20 years, but there is no obvious explanation for these age-related effects except in so far as the mechanisms of specific and non-specific resistance function less effectively at the extremes of life.

Hormonal Effects

Pregnancy had a very pronounced effect on the severity of smallpox. Especially in variola major, pregnant women were much more likely than any other category to suffer from haemorrhagic-type smallpox (see Chapter 1). Pregnant women have elevated levels of 17-dihydroxycorticosteroids, which have an anti-inflammatory effect, depress the immune

response and inhibit interferon production. Studies in rabbits infected with vaccinia virus showed that cortisone diminished the local inflammatory reaction and increased viral titres in the blood and internal organs (Bugbee et al., 1960). Vaccination could produce severe effects in humans receiving corticosteroid therapy.

Rao et al. (1968b) found that cortisone converted experimental smallpox in monkeys from a non-lethal into a lethal disease. Viraemia was greatly enhanced in intensity and persisted for a longer time, the internal organs contained much more virus than in control animals, and there were numerous haemorrhages in the lungs and in the mucous membrane of the gastrointestinal tract.

Interferon

Interferons are a family of proteins of low molecular weight produced by a wide variety of cells. Lymphocytes produce a different kind of interferon (gamma-interferon) from fibroblastic cells, but all kinds of interferon may render cells that take them up more resistant to viral infection. Vaccinia virus was the first virus shown to be sensitive to interferon in an intact animal. Isaacs & Westwood (1959) showed that interferon prepared in rabbit cells protected rabbits completely against intradermal infection with a large dose of vaccinia virus, when given a day before the virus was administered, and against a smaller dose when both were administered intradermally on the same day. However, Blanden (1970, 1971a) showed that passively administered interferon had no effect on recovery from mousepox. Interferon seems unlikely to have played a role in determining differential host responses in smallpox, but it may have been important in determining the differences in severity of inoculation smallpox and the "natural" disease.

Interferon and inoculation smallpox

Inoculation smallpox (variolation) is much milder than "natural" smallpox (see Chapters 1 and 6). Following the demonstration that vaccinia scabs contained interferon, Wheelock (1964) suggested that the presence of interferon in scab material that was used for variolation might have so interfered with the replication of the inoculated virus that the consequent disease was milder than smallpox acquired by the inhalation of virus contained in oropharyngeal secretions. This is unlikely to be the complete explanation; intradermal inoculation was associated with a shorter incubation period and the immune response would have been differently stimulated, but interferon in the inoculum and possibly the local production of interferon induced by inactivated virus in the inoculum may have played a role.

GENETIC ASPECTS OF RESISTANCE TO SMALLPOX

Because of the availability of lines of mice of known genotypes and of congenic recombinant strains (Klein, 1975), these animals are uniquely suitable for the analysis of genetic resistance to viral infection. Studies with mousepox (Briody et al., 1956; Schell, 1960a,b; Wallace et al., 1985) demonstrated that genetic factors played a major role in determining their response to mousepox.

It is clearly not possible to analyse the genetic component of the resistance of humans to smallpox in this way. Nevertheless, it is worth examining whether any human population groups showed unusual resistance or susceptibility, independent of the effects of vaccination.

Natural Selection for Resistance to Smallpox

Once again, an animal model may provide a useful lead in understanding what may have happened in smallpox. Myxomatosis, a severe generalized poxvirus disease in European rabbits (*Oryctolagus cuniculus*), provides the best example of rapid enhancement of the level of genetic resistance in a population as a result of exposure to the disease (Fenner & Ratcliffe, 1965; Fenner, 1983). Although it was nowhere near as lethal a disease as myxomatosis, smallpox was severe enough to have had a selective effect for resistance among humans exposed to infection over many centuries, as in India and China and to a lesser extent in Europe.

Reports of smallpox in the 16th and 17th centuries among the Indian tribes of North America (Stearn & Stearn, 1945) and in Brazil (Hemming, 1978) describe the extreme severity of smallpox in these hitherto unexposed

populations. Hemming notes that in Brazil the Portuguese colonists observed that Negro slaves, when they got smallpox, suffered less severely than the Amerindian slaves; most of the European invaders themselves were immune because of infections sustained in their childhood. Although several other factors besides lack of genetic resistance could have been involved in exacerbating the effects of the disease among the Amerindians - notably the severe social disruption accompanying the first outbreaks—it is tempting to consider that their extreme susceptibility was in part related to the absence of previous selection for resistance to smallpox.

From what we now know about the relation between the major histocompatibility genes and resistance to viral infections (review: Zinkernagel, 1979), it would have been interesting to investigate the relation between HLA groups and susceptibility to smallpox; experiments with mousepox showed that at least part of the genetic resistance to this disease was associated with the H-2 complex in the mouse (R.V. Blanden, personal communication, 1981). The opportunity to do this never arose, but Vries et al. (1977) showed that after vaccination with vaccinia virus, the lymphocytes of Dutch soldiers belonging to a particular HLA group (Cw3) responded significantly less effectively than others in an *in vitro* lymphocyte transformation test using vaccinia virus as antigen (a measure of cell-mediated immunity). This HLA group made up 30% of the general population in the Netherlands, compared with 83% of the low-responder group.

During the 1950s and 1960s, a great deal of information was accumulated on the distribution of ABO blood groups in different populations. Pettenkofer et al. (1962) claimed that there was a correlation between past histories of smallpox epidemics and the distribution of ABO blood group frequencies, and that in India there were different degrees of scarring in persons of blood groups B and O compared with those of blood groups A and AB. However, investigations by several different teams of workers in India (Bhattacharyya et al., 1965; Downie et al., 1965b; Helmbold et al., quoted by Vogel & Chakravartti, 1966; Sukumaran et al., 1966), in Brazil (Krieger & Vicente, 1969), and in Zaire (Lambotte & Israel, 1967) found no evidence of a correlation between the incidence and severity of smallpox and the ABO blood group of the subjects. Nor was there any correlation between ABO blood groups and the occurrence of neurological or dermal complications of vaccination (Gurvich et al., 1980). Most human geneticists now doubt whether smallpox was an important selective agent in blood group ABO polymorphism (Mourant et al., 1978).

SUMMARY: THE PATHOGENESIS OF SMALLPOX

Although a good deal of speculation and extrapolation from various model systems will inevitably be involved, it is worth attempting to summarize the results of the work presented in this chapter in the form of a comprehensive picture of the pathogenesis of smallpox in man.

Viral Entry and Infection

Infection usually occurred by the implantation on the oropharyngeal or respiratory mucosa of virus released from lesions in the mouth, nose and pharynx into the nasal and oropharyngeal secretions of the source case during the first week of rash. Such material probably consisted of well-dispersed virions and would have been relatively free of interferon. In contrast, scab material usually consisted of large fragments of inspissated material with infectious virions bound within a dense, hard fibrin mesh, which contained a substantial amount of interferon, and from which it was difficult to release virus except by mechanical grinding. These features probably accounted for the much lower transmissibility associated with scabs, compared with oropharyngeal secretions.

The initial site of lodgement was usually somewhere in the oropharynx, nasopharynx or the lower respiratory tract. Whatever cells were initially infected, macrophages would soon have become infected and by about the 3rd day would have entered the lymphatics and thus reached the regional lymph nodes. They might also have entered the bloodstream at this stage, or in any case by about the 4th day, after a brief delay and replication in the draining lymph nodes.

The initial infection in the oropharynx or respiratory tract was silent, producing neither symptoms nor a local lesion that could be recognized clinically, or by autopsy in cases that died early.

Spread through the Body

The inevitable lack of careful postmortem examinations of cases of smallpox dying from other causes during the incubation period of the disease, combined with the paucity of careful postmortem or virological examinations of acutely fatal cases, makes it difficult to assess precisely where the virus replicated before the secondary viraemia occurred, at the time of the onset of symptoms. The most likely places were the lymphoid organs (spleen, bone marrow and lymph nodes), but extensive necrosis did not occur there. Viraemia was largely cell-associated and most virions that existed free in the plasma were probably in the enveloped form.

The reasons for the localization of virus in the skin and the characteristic "centrifugal" distribution of the rash are unknown. Probably, infected macrophages migrated from small vessels in the dermis into the epidermis, where they proceeded to cause infection of the cells of the Malpighian layer. Oedema and ballooning degeneration followed, with reticulating degeneration and splitting of the epidermis that produced a multiloculated vesicle. Later there was a migration of polymorphonuclear cells into the lumen of the developing vesicle, so that its contents became pustular.

The Immune Response

The early lodgement of infected macrophages in the lymph nodes, bone marrow and spleen would have stimulated an immediate immune response to the wide variety of viral antigens produced by infected cells. The first component of the immune system to become manifest was the production of cytotoxic T cells, which, because of their affinity to the early viral antigens found in the cell membranes, promptly destroyed many infected cells before they produced virions. Later, neutralizing antibodies appeared, some of which were directed against the viral envelope (which contained several of the antigens also found in the surface membrane of infected cells); others were able to neutralize the infectivity of intracellular non-enveloped virions, which were released when necrotic cells were disrupted. The activity of cytotoxic T cells and the titre of antibodies increased as time progressed. In addition, infected macrophages and lymphocytes, as well as infected cells in the skin, produced interferon. In cases in which the early cellular immune response was vigorous, replication of the virus was inhibited and the skin lesions were restricted, so that a discrete rash developed.

If the cellular immune response was grossly deficient, the case may have presented as flat-type smallpox. Haemorrhagic-type smallpox was associated with unrestricted replication of the virus especially in the bone marrow, so that a much higher viraemia developed than in most non-haemorrhagic cases and megakaryocyte destruction in the bone marrow led to defects in the blood coagulation mechanism. Further, the immune response, both humoral and cellular, was defective in haemorrhagic-type smallpox, which was particularly frequent in pregnant women, probably because of their increased corticosteroid secretions.

Death or Recovery

The outcome of the infection was either death or recovery, with or without sequelae. Except in haemorrhagic-type smallpox, the cause of death was obscure, since none of the "vital organs" (brain, lungs, heart, kidneys, liver) seemed to have been severely damaged in fatal cases. It was ascribed to severe toxaemia, perhaps due in part to the effect of circulating immune complexes. Death in very severe cases (confluent ordinary, flat and haemorrhagic types) was associated with a high and prolonged viraemia and a poor humoral antibody response, and probably a defective cellular immune response as well.

The commonest sequelae were pockmarks, which could occur all over the body but were usually most profuse on the face because of the large number of sebaceous glands there and the deeper pitting associated with their involvement. Encephalitis, with a pathogenesis as obscure as that of postvaccinial encephalitis, occurred in about 0.2% of cases of variola major. It was somewhat rarer in variola minor, but a relatively more important cause of death in that disease.. Arthritis and osteomyelitis sometimes occurred, though often they were recognized only after recovery. Blindness was an important but rare complication, usually occurring in cases in which there was malnutrition and/or secondary bacterial infection.

Recovery was accompanied by long-lasting immunity to reinfection with variola virus. Heterologous immunity—e.g., to vacci-

nation—was much less prolonged, especially in cases of variola minor. Variola virus did not persist in the body after recovery; thus, previously infected persons, even when immunosuppressed, have shown no recurrence of infectivity.

CHAPTER 4

THE EPIDEMIOLOGY OF SMALLPOX

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INTRODUCTION

Chapters 1 and 3 were concerned with smallpox as a disease of individual human beings, discussing such problems as how the virus entered the body and spread through it, how the body reacted and what symptoms were produced, and how the virus was shed. Since smallpox was an infectious disease, there is another dimension to its study besides its effect on individual patients—namely, its behaviour in human populations. This di-

mension constitutes the epidemiology of the disease, which involves examination of the incidence of smallpox and the mortality attributable to it, over time and in different countries and regions; the various determinants of its occurrence and spread; its maintenance as an endemic disease; and the causes of epidemics. These considerations were of fundamental importance in its control and eventual eradication.

THE MORBIDITY AND MORTALITY OF SMALLPOX IN THE 20TH CENTURY

In Chapter 5 we describe how smallpox spread throughout the world, first through Asia, beginning in the 1st century AD, and then into Europe and northern Africa from about AD 700 onwards. With European colonization the disease was carried to Central, South and North America and southern Africa in the 16th and 17th centuries. By the time vaccination was introduced, at the end of the 18th century, the distribution of smallpox was world-wide. It was endemic everywhere, except in remote areas with sparse populations, such as Australia, New Zealand and the islands of the Pacific, Atlantic and Indian Oceans. Periodically it caused disastrous epidemics in many smaller island communities and then died out, as, for example, in Iceland, the islands of the Caribbean, Hawaii, Tahiti, Mauritius and the smaller islands of what were then the Netherlands East Indies (Hirsch, 1883).

Secular Changes in the Global Occurrence of Smallpox

By the early years of the 20th century endemic smallpox had been eliminated from a few of the countries of northern Europe with small populations, although importations from more densely populated neighbouring countries occurred almost every year (see Chapter 8). However, until current statistics began to be published by the Health Organisation of the League of Nations in 1922 (Howard-Jones, 1975), there was no mechanism for systematically collecting and disseminating information on the incidence of smallpox in different countries. National data for the early years of the 20th century were compiled by Low (1918) and consolidated figures for the years 1920–1947 were published by the Interim Commission of the World Health Organization (Fabre, 1948).

Weekly and consolidated annual figures for reported cases of smallpox in different countries were published by the World Health Organization after 1948. These figures, supplemented by investigations carried out by the WHO Smallpox Eradication unit, were used for the tabulation of reported cases of smallpox by country and by WHO region provided in the *Final Report of the Global Commission for the Certification of Smallpox Eradication* (World Health Organization, 1980). Further supplemented by studies conducted by the authors of the present book, these data were used for the detailed tabulation of reported cases of smallpox in the larger countries of the world presented in Chapter 8. These official data reflect only reported cases, and, as will be shown in a later section, smallpox was grossly underreported in most countries. The figures convey an impression of the ebb and flow of the disease in various countries, but they give little idea of its true incidence.

More relevant in the present context is a global overview of secular trends in the numbers of countries in which smallpox was endemic during the period from 1920 until its eradication (Fig. 4.1). To obtain the data for this, all available sources of information were consulted, and the assumption was made that smallpox was persistently endemic between the 1920s and the 1940s in countries in which in the 1950s it appeared to be a long-established endemic disease, even though some of these countries had failed to report its occurrence to the Health Organisation of the League of Nations during that period. The data are plotted by 5-year intervals prior to 1958 and annually thereafter; they show for each continent the secular changes in the numbers of countries in which smallpox was endemic. In terms of the global eradication of smallpox, important administrative decisions were taken in 1959, when the World Health Assembly first launched a programme for global eradication, and in 1967, when the Intensified Smallpox Eradication Programme was initiated (see Chapters 9 and 10).

The period 1920–1958

In 1920 smallpox was endemic in most countries, being present in 124 and absent

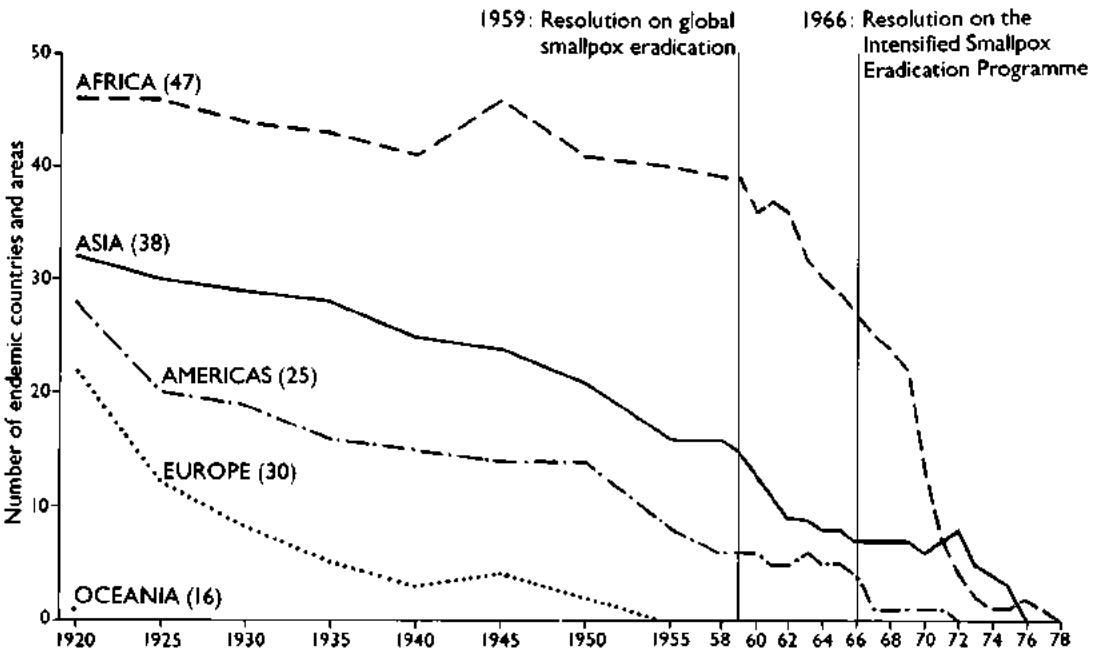

Fig. 4.1. Numbers of countries and territories in which smallpox was endemic between 1920 and 1978, arranged by continent. The figures in brackets indicate the numbers of countries and territories involved. Their names (as of 1986) are listed below.

Africa: Algeria, Angola, Benin, Botswana, Burkina Faso (Upper Volta), Burundi, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Djibouti, Egypt, Equatorial Guinea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Libyan Arab Jamahiriya, Madagascar, Malawi, Mali, Mauritania, Morocco, Mozambique, Namibia (South West Africa), Niger, Nigeria, Rwanda, Senegal, Sierra Leone, Somalia, South Africa, Sudan, Swaziland, Togo, Tunisia, Uganda, United Republic of Tanzania, Zaire, Zambia, Zimbabwe.

Americas: Argentina, Belize, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, French Guiana, Guatemala, Guyana, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, USA, Uruguay, Venezuela.

Asia: Afghanistan, Bahrain, Bangladesh, Bhutan, Burma, China, Democratic Kampuchea, Democratic Yemen, Democratic People's Republic of Korea, Hong Kong, India, Indonesia, Islamic Republic of Iran, Iraq, Israel, Japan, Jordan, Kuwait, Lao People's Democratic Republic, Lebanon, Loro Sae (East Timor), Macao, Malaysia, Mongolia, Nepal, Oman, Pakistan, Philippines, Qatar, Republic of Korea, Saudi Arabia, Singapore, Sri Lanka, Syrian Arab Republic, Thailand, United Arab Emirates, Viet Nam, Yemen.

Europe: Albania, Austria, Belgium, Bulgaria, Cyprus, Czechoslovakia, Denmark, Finland, France, German Democratic Republic, Federal Republic of Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden, Switzerland, Turkey, USSR, United Kingdom, Yugoslavia.

Oceania: Australia, Fiji, French Polynesia, Guam, Kiribati, Mariana Islands, Marshall Islands, Nauru, New Caledonia, New Zealand, Papua New Guinea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu.

only from all the countries of Oceania and 16 countries in the other 4 continents. The only countries of Oceania with populations large enough to have supported endemic smallpox were Australia and New Zealand, which were protected by distance and an effective system of seaport quarantine from all but a very few importations, most of which were controlled at the port of entry.

By 1920 endemic smallpox in Europe had been eliminated only from Denmark, the Netherlands, Norway and Sweden. Subsequently the situation improved quite rapidly, so that by 1935 endemic smallpox had been eliminated from 25 countries, although it remained relatively common in Portugal, Spain, the USSR and the United Kingdom. The last endemic case in the USSR was reported in 1936 (see Chapter 8). Elsewhere in Europe the downward trend continued, and the continent was free of endemic smallpox by 1953.

In the Americas, tens of thousands of cases of smallpox were reported annually up to the late 1930s, variola major in Mexico and some South American countries and mostly variola

minor in other South American countries and the USA. Smallpox was eliminated from the Central American countries between 1920 and 1951 and from Mexico in 1951. Endemic variola major had been eliminated from the USA in 1926 but variola minor persisted until the late 1940s. Smallpox continued to be endemic in the larger countries of South America until 1950, when a steady decline began. In that year a regional eradication campaign for the Americas was initiated by the Pan American Sanitary Organization (later renamed the Pan American Health Organization) (see Chapter 9) and the incidence continued to fall until, by 1958, smallpox remained endemic in only 6 countries.

The situation was not nearly as good as this in Asia and Africa, the continents in which reporting was the least reliable. The number of endemic countries in Asia declined slowly, endemic smallpox being eliminated from Indonesia, Malaysia, the Philippines and Sri Lanka by 1938, only to be reintroduced into these countries during the disruption caused by the Second World War. After that there was a slight but steady improvement, mainly in the smaller countries of eastern Asia, but the disease appeared to be largely unchecked in the Indian subcontinent and was still endemic in some 40% of the countries of Asia in 1958.

In Africa progress was even slower, except for the gradual reduction in the number of reported cases and the elimination of endemic smallpox in the countries of northern Africa and some of the small sparsely populated countries in southern Africa. During this period successful country-wide elimination did not always mean that subsequent importations would be successfully contained. For example, after the elimination of endemic smallpox from Egypt in the mid-1930s, variola major was reintroduced during the Second World War and became endemic again, producing several thousand reported cases in 1943–1945 (Tulloch, 1980). There were similar exacerbations after the Second World War in Algeria, Libya and Morocco. In most countries in Africa south of the Sahara smallpox was apparently almost as common in 1958 as it had been two decades earlier.

The period 1959–1966

In 1959 the Twelfth World Health Assembly adopted a resolution introduced by the USSR calling for the world-wide eradication of smallpox (see Chapter 9), confident in the knowledge that eradication had by then been achieved in Europe and in North and Central America. The situation in South America appeared to be manageable, and indeed the number of endemic countries decreased until, by 1967, smallpox remained endemic only in Brazil. The real problem was posed by the developing countries of Africa and Asia. During the few years between 1959 and 1966 there were substantial gains in Asia, the most important of which was the elimination of endemic smallpox from China. This was achieved by 1961 and was due entirely to a national initiative. Smallpox, however, remained rampant in the Indian subcontinent. Some progress was made in western and southern Africa, but in 1966 the disease was still endemic in 27 of the 47 countries of Africa.

The period 1967–1978

As outlined in Chapter 9, by 1967 it was clear that—the Twelfth World Health Assembly resolution notwithstanding—the global eradication of smallpox could not be achieved without greater financial, administrative and scientific support. In that year the Intensified Smallpox Eradication Programme was instituted, supported by funds from the WHO regular budget, and a Smallpox Eradication unit was established at WHO Headquarters in Geneva. At the same time, the WHO regional offices responsible for countries in which endemic smallpox was present assumed an active role in organizing and coordinating country programmes. The rapid fall in the number of countries with endemic smallpox over the period 1967–1978 is illustrated in Fig. 4.1 and described at greater length in Chapter 10.

By the time that the Intensified Programme was launched, smallpox had been eradicated in South America, except for Brazil, in which the last case in the Americas occurred in 1971. Results were achieved rapidly in the countries of western and central Africa in a campaign which began in 1967. Steady progress occurred in eastern, southeastern and southern Africa. The biggest challenge confronting the Intensified Smallpox Eradication Programme was the eradication of variola major from the Indian subcontinent, a relatively slow process, which was, however, achieved by 1975. By 1976 the only remaining endemic country was Ethiopia, in

which variola minor persisted and spread to Somalia, eventually to be eradicated from the Horn of Africa, and the world, by the end of 1977.

Smallpox Incidence and Incidence Rates

General considerations

The countries and territories listed beneath Fig. 4.1 vary enormously in size and population, from China and India on the one hand, each with populations of several hundred millions, to Bahrain and Swaziland, with populations of a few hundred thousand, on the other.

The numbers of cases of smallpox reported annually to the international health authorities by the governments of different countries varied greatly in accuracy. Those obtained from non-endemic countries with well-established health services, reporting small outbreaks due to importations, were probably the most accurate, although even here distortions sometimes occurred, owing to the suppression of reports (see Chapter 23). The reported numbers of cases in endemic countries for the earlier years of the period under review—often countries with grossly inadequate reporting systems—greatly understated the true incidence of the disease. Even in countries in which smallpox was an important public health problem and there were reasonable health services, reporting was incomplete before and even after national eradication campaigns had been launched (see below). However, the incidence of reported cases (Fig. 4.2) provides some indication of the true incidence of smallpox in the countries in which it was endemic in 1967. At the start of the Intensified Smallpox Eradication Programme, the reported incidence amounted to perhaps 1–2% of the true figure.

During the Intensified Programme several efforts were made to determine what proportion of cases was actually reported in countries with endemic smallpox. Two kinds of assessment were made. The first contrasted the reported figures with the incidence as estimated by pockmark surveys carried out in selected age groups; the second was based on a comparison, in India and Ethiopia, of the reported incidence before and after efficient surveillance and case-reporting systems were established, during the late stages of the eradication campaigns in each country.

Assessment by facial pockmark surveys

First employed by Dr Jacobus Keja in Nepal and then in Indonesia (see Chapter 13), this method was later used by Foster (WHO/SE/72.34) and Hughes et al. (1980) for assessing the efficiency of reporting in western Africa and Bangladesh respectively. The method involved the examination of persons in appropriate age groups for facial pockmarks (Table 4.1). For survey purposes a

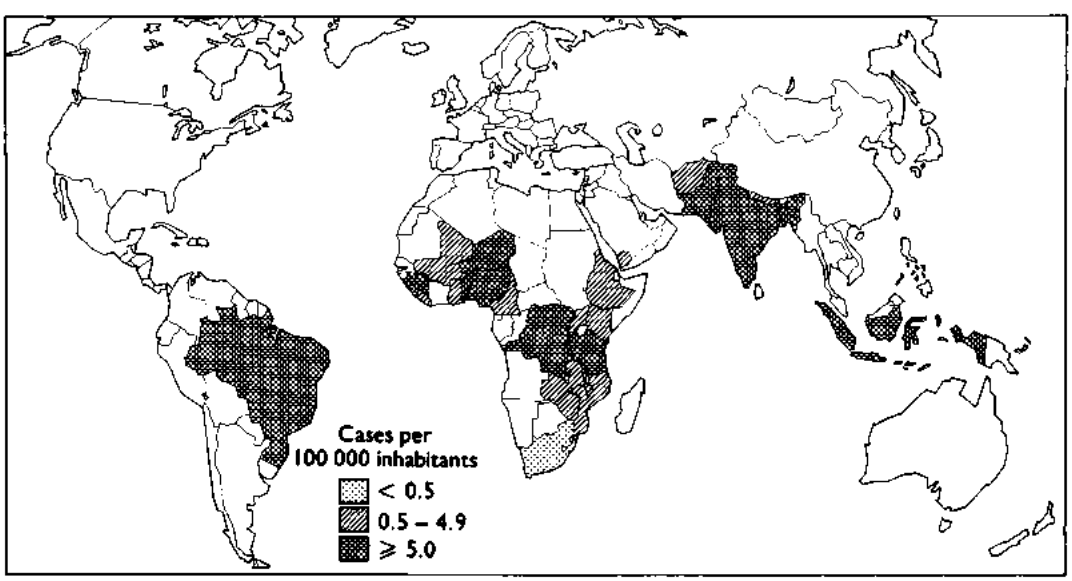

Fig. 4.2. Incidence of reported cases in the 31 countries and territories in which smallpox was endemic in 1967.

Table 4.1. Efficiency of reporting of smallpox in Kano (an urban area in Nigeria), as estimated from facial pockmark surveys in the age group 0–14 years[a]

(1) *Estimated population in the age group 0–14 years*
Total population—500 000, of which 223 000 (44.6%) were 0–14 years old.

(2) *Estimation of total number of cases of smallpox in the age group 0–14 years*
Observed frequency of smallpox pockmarks in a sample survey of the age group 0–14 years—3.7%.
Estimated number of children aged 0–14 years with facial pockmarks—$3.7/100 \times 223\,000 = 8250$.
Proportion of children aged 0–14 years who retained pockmarks for at least 1–4 years—55%.
Estimated number of children aged 0–14 years who had smallpox and survived—$\frac{8250}{55/100} = 15\,000$.
Smallpox case-fatality rate in children aged 0–14 years—13%.
Estimated total number of cases of smallpox in the age group 0–14 years—$\frac{15\,000}{87/100} = 17\,250$.

(3) *Estimation of total number of cases of smallpox during the last 15 years*
Proportion of smallpox cases which normally occur in the age group 0–14 years—50%.
Estimated total number of smallpox cases during the last 15 years—$\frac{17\,250}{50/100} = 34\,500$.

(4) *Calculation of the efficiency of reporting smallpox*
Reported number of smallpox cases during the last 15 years—2805.
Reporting efficiency—$\frac{2\,805}{34\,500} = 8.1\%$.

[a] Based on Foster (WHO/SE/72.34).

positive case was defined as one which had at least 5 characteristic round, depressed facial scars, a millimetre or more in diameter. By correcting for the observed rate of smallpox mortality in a selected age group, for mortality due to other causes and for the disappearance of facial scars over time (which varied according to the age at which the person acquired smallpox and was determined for each age group and area) it was possible to estimate the incidence rates of smallpox within the sampled population. The smallpox incidence in the entire population could be estimated by correcting for the age distribution of cases, and this figure could then be compared with the number of officially reported cases.

Using this procedure, Foster calculated that the efficiency of reporting was 1.3% in rural areas of Nigeria and 8.1% in Kano, an urban centre. Hughes et al. (1980), using a similar procedure, found that as late as 1972 reporting efficiency in Bangladesh was only about 12%, but rose in the succeeding years, when active searches for unreported cases were intensified, to over 80% (see Chapter 16, Fig. 16.9). The health services in Bangladesh and Nigeria were more extensive and better developed than those in most endemic countries at that time, so that these estimates reflect better-than-average situations.

Changes in the numbers of reported cases after improved surveillance

The highest numbers of cases for many years were often reported during the periods just before country-wide elimination was achieved, since by this time good surveillance systems were in operation. For example, the highest figure for India since the 1950s was 188 003 in 1974, the year before the attainment of eradication. The results of active searches in India in 1973 (Fig. 4.3), described in detail in Chapter 15, suggested that at that time the reporting efficiencies in the highly endemic states of Madhya Pradesh and Uttar Pradesh were less than 1% and 5% respectively—and this a decade after the launching of the Indian national smallpox eradication programme and 6 years after the initiation of the Intensified Smallpox Eradication Programme. Likewise, with the development of

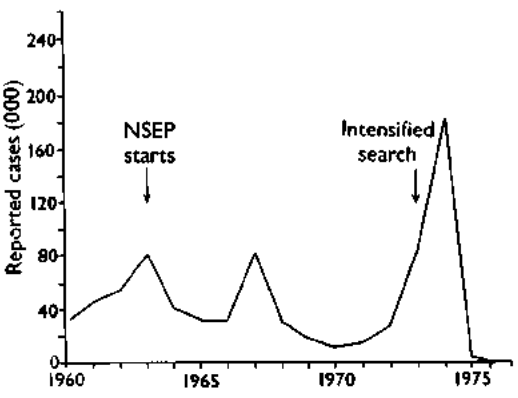

Fig. 4.3. Evidence of the underreporting of variola major. Increase in the number of reported cases in India following the introduction of active searches in the highly endemic states in 1973 (see also Chapter 15, Fig. 15.15). NSEP = National Smallpox Eradication Programme of India.

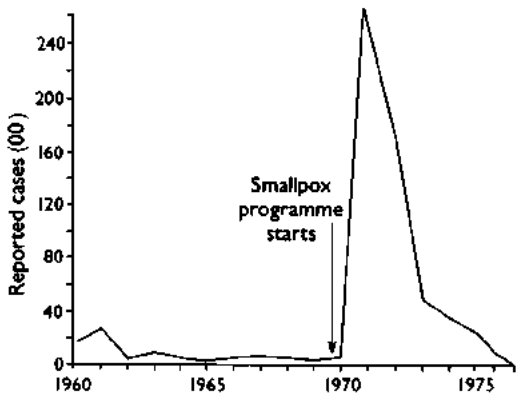

Fig. 4.4. Evidence of the underreporting of variola minor. Increase in the number of reported cases in Ethiopia following the initiation of intensified surveillance in 1971.

better surveillance in Ethiopia in 1971 (see Chapter 21), there was a dramatic increase in the number of reported cases, 722 being notified in 1970 and 26 329 in 1971 (Fig. 4.4).

For China, the most populous country in the world, with endemic variola major for centuries and poor vaccination coverage prior to 1950, the cases reported to the international health authorities were in the thousands only, the highest figure (68 101) being reported in 1951, just after the national eradication campaign had been launched.

The overall picture

It is clear that the reporting of cases of smallpox was the most efficient in countries in which the health services were well developed, which was usually where the disease was least common. It was very inefficient elsewhere. Since the countries in which reporting was good must have provided only a small proportion of the total number of cases in the world, it is not unreasonable to regard the official figures reported to WHO as representing only 1–2% of the true incidence—probably nearer 1% for the years before the initiation of the global eradication programme. In the early 1950s, 150 years after the introduction of vaccination, there were probably some 50 million cases of smallpox in the world each year, a figure which had fallen to perhaps 10–15 million by 1967, when the disease had already been eliminated in 125 of the 156 countries and areas listed in the legend of Fig. 4.1.

The Effect of Vaccination on the Incidence of Smallpox

As has been described in Chapter 1, an attack of smallpox in persons who had been vaccinated was usually less severe than in the unvaccinated. Much more important, from the point of view of the ultimate eradication of smallpox, was the fact that vaccination within the previous 5 years usually completely prevented disease. Some vaccinated persons experienced subclinical infections, as judged by their serological responses (Heiner et al., 1971a). These subjects did not transmit the disease to others, although the subclinical infection substantially increased their level of immunity. Even if their immunity had not been boosted by subclinical infection or revaccination, many vaccinated individuals were protected against clinical smallpox for a much longer period than 5 years. However, no data exist which allow an accurate assessment to be made of the proportion of those at risk who were protected against smallpox at various intervals after vaccination. Such data as are available suggest that vaccination in infancy protected most of those under 10 years of age and at least half of those aged 10–20 years from overt disease.

Case-Fatality Rates in Smallpox

Data from the Indian subcontinent show that Asian variola major had always been a disease with a high case-fatality rate, of the order of 20% or more in unvaccinated persons. Higher case-fatality rates were observed in urban hospitals than in the population as a whole, as documented in Bangladesh (Koplan et al., 1978; see Chapter 1), and in cities than in rural areas (see Table 4.6). Historical documents suggest that high case-fatality rates had prevailed everywhere in the world for many centuries. Indeed, epidemics in previously unexposed, subsistence-farming populations appeared often to have produced much higher mortalities than those seen in Asia, owing to the social disruption and consequent starvation that they caused.

From about the end of the 19th century another variety of smallpox, variola minor, was recognized, which although it produced similar skin lesions had a case-fatality rate of only about 1% (see Chapter 1). Subsequently, observations made in Africa during the Inten-

sified Smallpox Eradication Programme suggested that smallpox of intermediate severity, with case-fatality rates of 5–15%, was endemic in many parts of that continent.

In addition to differences in the virulence of the virus, several other important variables can be identified that played a role in the observed variations in case-fatality rates: the age distribution of cases, the effects of previous vaccination, nutritional status, and the influence of reporting accuracy, since severe (hospitalized) cases and deaths were more likely to be reported than milder cases. Pregnant women were especially susceptible and showed higher case-fatality rates for both variola major and variola minor than did men and non-pregnant women of the corresponding age groups (see Chapter 1). Further, there were interactions between age and vaccination status, since in persons receiving only primary vaccination, susceptibility increased with the interval since vaccination and thus with age. Relevant data from India and from western and central Africa are set out in Tables 4.2 and 4.3.

Foege et al. (1975) noted that the age distribution of cases in western and central Africa in 1968 followed closely the age distribution of the population, reflecting the predominant occurrence of cases in isolated and poorly vaccinated rural areas. In India, on the other hand, with its much denser and more mobile population, smallpox was predominantly a disease of children (over 70% of cases in individuals under the age of 15 years: Table 4.2); the situation was similar in Bangladesh, Burma, Indonesia and Pakistan. Since the immunity produced by vaccination in childhood steadily waned, the majority of cases in vaccinated subjects occurred in older age groups (54.3% in persons over 14 years of age: Table 4.3), whereas in unvaccinated subjects 82.3% of cases occurred in children less than 15 years old. The age-related trends in case-fatality rates were similar in India and Africa, the rates being highest in the very young and in older persons. Children and adolescents (10–19 years of age) had lower case-fatality rates than any other age group, a feature which was accentuated when only

Table 4.2 Age distribution and case-fatality rates of smallpox in India and in western and central Africa[a]

India, 1974–1975[b]				Western and central Africa, 1968[c]			
Age group (years)	Cases		Case-fatality rate (%)	Age group (years)	Cases		Case-fatality rate (%)
	Number	%			Number	%	
<1	1 373	5.8	43.5	<1	102	4.8	29.4
1–4	5 867	24.9	24.5	1–4	417	19.6	11.5
5–14	9 501	40.4	11.4	5–14	494	23.2	7.7
15–39	5 698	24.4	9.0	15–44	1 009	47.5	15.2
40–49	695	2.9	20.1	⩾45	103	4.8	32.0
⩾50	412	1.7	37.4				
Total	23 546	100	17.4	Total	2 125	100	14.2

[a] Includes both vaccinated and unvaccinated subjects.
[b] Based on Basu et al. (1979).
[c] Based on Foege et al. (1975).

Table 4.3 Age distribution and case-fatality rates of smallpox in vaccinated and unvaccinated subjects in 6 states of India, 1974–1975[a]

Age group (years)	Vaccinated			Unvaccinated		
	Cases		Case-fatality rate (%)	Cases		Case-fatality rate (%)
	Number	%		Number	%	
0–4	114	13.3	10.5[b]	725	36.8	45.7
5–14	277	32.4	5.1	897	45.5	12.4
15–39	348	40.7	4.9	265	13.4	20.7
⩾40	116	13.6	8.6	84	4.3	29.8
Total	855	100	6.2	1 971	100	26.5

[a] Based on Basu et al. (1979).
[b] Thought to be cases vaccinated during the incubation period.

unvaccinated subjects were considered. However the data are analysed, the case-fatality rates were higher in India than in western and central Africa. Nevertheless, the age distribution of cases clearly influences the overall case-fatality rate for a particular geographical region, and critical comparisons of geographical variability in case-fatality rates would have to assess separately the figures for vaccinated and unvaccinated subjects and consider the age distribution of cases of smallpox. Unfortunately, there are very few large series of cases, from different geographical areas, that give such details; the analyses that follow are the best available.

Shafa (WHO/SE/72.35) analysed data from 11 areas for which he considered that reasonably reliable information was available, making adjustments for age-specific case-fatality rates by adjusting the data to a standard age distribution. The case-fatality rates for 9 areas in which variola major was endemic are shown in Table 4.4. They were always higher among infants and children aged 0–4 years than among individuals in older age groups.

Table 4.4 Case-fatality rates of variola major in different geographical areas for the total population and the age group 0–4 years[a,b]

Country or area	Age group	
	0–4 years (%)	All ages (%)
Bangladesh[c]	47	36
	26.8	18.5
India (Tamil Nadu)	43	26
Burma	23	17
Afghanistan	19	16
India (Punjab)	18	15
Indonesia (Jakarta)	16	13
Indonesia (West Java)	11	8
West Africa	14	13
Togo	10	8

[a] Based on Shafa (WHO/SE/72.35).
[b] Includes both vaccinated and unvaccinated subjects.
[c] More recent data (Joarder et al., 1980) suggest that the lower figures (26.8% and 18.5%) represent more accurately the true situation in Bangladesh.

The effect of age on mortality was even more pronounced in variola minor, in both Brazil and Africa, in which the case-fatality rate was much higher for infants (less than 12 months old) than for any other age group (Table 4.5). Indeed, in Brazil, in which data were available for infants less than 3 months old, the case-fatality rate in this group was 16.7%.

Geographical variations in crude case-fatality rates, based on data obtained during the Intensified Smallpox Eradication Programme, are shown in Table 4.6. There are striking differences between the case-fatality rates in large cities and those in the surrounding countryside (see Indonesia and Pakistan). This may have been due partly to the better recording of deaths and partly to the fact that data for the cities were derived in large measure from hospitals, in which more severe and neglected cases were more common (Koplan et al., 1978).

There are also large differences between the case-fatality rates in countries in which variola minor was endemic and those in other countries. Variola minor itself varied in severity, the form present in Botswana in 1972 (which may have been characteristic of "amaas" of southern Africa) being particularly mild. Smallpox other than variola minor was associated with case-fatality rates that varied in different geographical areas from slightly more than 5% to over 20%. There were suggestions in the mid-1960s that strains of virus from eastern African countries (Uganda and the United Republic of Tanzania) could be differentiated from Asian strains of variola major virus by laboratory tests, and it was suggested that the disease there should be called "variola intermedius". However, the "characteristic" laboratory reactions of "variola intermedius" were not invariable for strains from that area, and case-fatality rates only slightly higher than those found in eastern Africa were also recorded for Indone-

Table 4.5 Age-specific case-fatality rates in variola minor (data collected during the Intensified Smallpox Eradication Programme)

Age group (years)	Brazil (1968–1969)		Botswana (1971–1972)		Ethiopia (1971–1976)		Somalia (1977)	
	Number of cases	Case-fatality rate (%)	Number of cases	Case-fatality rate (%)	Number of cases	Case-fatality rate (%)	Number of cases	Case-fatality rate (%)
<1	387	5.2	17	5.9	1 322	7.9	47	12.8
1–4	2 322	0.7	195	0.5	13 501	1.8	506	0.6
5–14	4 389	0.2	505	0.0	26 087	0.6	1 061	0.1
⩾15	2 683	1.0	365	0.0	14 081	2.5	1 408	0.1
Total	9 781	0.7	1 082	0.2	54 991	1.5	3 022	0.4

Table 4.6 Case-fatality rates of smallpox in different geographical areas (data from country reports submitted prior to certification of eradication of smallpox)[a]

Country or area[b]	Period	Number of cases[b]	Number of deaths[b]	Case-fatality rate (%)[b]
Variola major: Asia				
Bangladesh	1975	1 127	209	18.5
India	1974–1975	23 546	4 103	17.4
Afghanistan[c]	1969–1973	1 898	306	16.1
Pakistan (Sind Province)	1972–1974	17 491	1 646	9.4
Pakistan (Karachi)	1973–1974	*587*	*140*	*23.9*
Indonesia (West Java)	1969	11 966	930	7.8
Indonesia (Jakarta)	1968	*405*	*82*	*20.2*
Variola major: Africa				
West Africa	1967–1969	5 628	540	9.6
United Republic of Tanzania	1967	1 629	150	9.2
Uganda	1966–1970	1 045	54	5.2
Variola minor: South America				
Brazil	1966–1969	9 854	75	0.8
Variola minor: Africa				
Ethiopia	1971–1976	54 991	838	1.5
Sudan	1970–1972	3 019	35	1.2
Somalia	1977	3 022	12	0.4
Botswana	1972	1 059	2	0.2

[a] Includes both vaccinated and unvaccinated subjects.
[b] Data in italics refer to urban areas.
[c] Excluding cases due to variolation.

sia and western Africa. As has been suggested in Chapters 1 and 2, it is possible to differentiate between variola major and variola minor by considering clinical features and epidemiology and, for some strains, the laboratory characteristics of the virus, but it is not worth while to attempt to designate "variola intermedius" or to differentiate further between strains of variola major. The data shown in Tables 4.4 and 4.6 illustrate the fact that both variola major and variola minor were caused by strains of variola virus which differed in their virulence for man, and that some strains were predominant in some geographical areas and other strains in other areas.

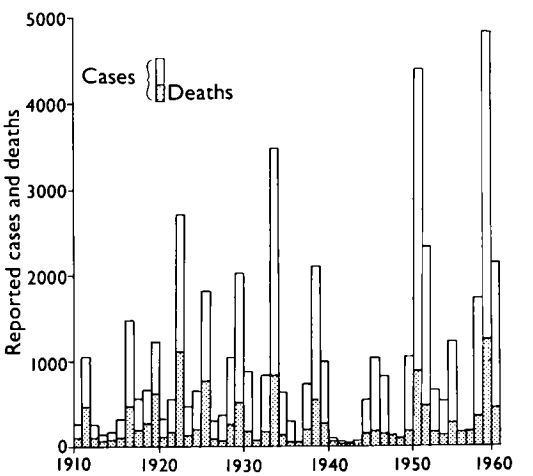

Fig. 4.5. Cyclic fluctuation in the incidence of smallpox in the city of Madras, India: annual numbers of cases and deaths between 1910 and 1960. (Based on Rao et al., 1960.) A similar cyclic fluctuation, with epidemics every 5–10 years, occurred in India as a whole and most other countries in which smallpox was endemic. (See Chapter 5, Fig. 5.2 and Chapter 6, Fig. 6.1.)

Smallpox Epidemics in Endemic Countries

It was widely observed that in countries in which smallpox was endemic there were periodic episodes of much higher incidence: "epidemic years". The history of smallpox before the 20th century is replete with accounts of great epidemics occurring against a background of endemic smallpox (see Chapter 5). An unusually complete series of data on smallpox incidence in the Åland Islands, Finland, extending from 1751 to 1890, showed a 7-year cycle of epidemics in the 18th century, which changed to an 8-year cycle, with a higher proportion of cases among adults, after vaccination became available in 1805 (Mielke et al., 1984). The phenomenon of epidemic years is well illustrated by more recent data from India. In the city of Madras, for example, Rao et al. (1960) found that there was a regular peaking of incidence every 4–6 years, epidemics extending over a period of 3 years, the middle year being the peak year (Fig. 4.5). This periodic

behaviour is a consequence of the size of the pool of susceptible individuals in the population and the rate of their removal by infection or vaccination. The phenomenon occurs in all common infectious diseases in which infection is followed by long-lasting immunity; it has been exhaustively analysed in measles (Bartlett, 1957) and is critically dependent on the rate of addition of new susceptible individuals to the population. A factor which lengthened the interval between epidemics of smallpox was that the occurrence of an epidemic led to greatly increased vaccination rates, because of increased activity by public health officials and increased demand for vaccination by the general public.

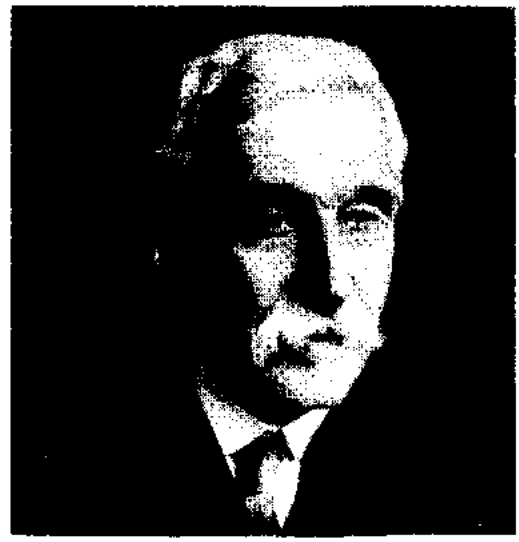

Plate 4.1. Sir Leonard Rogers (1868–1962). Distinguished British physician who worked in India for many years and was Professor of Pathology at Calcutta Medical College from 1900 to 1920. Besides making important contributions to many aspects of tropical medicine, he devoted particular attention to a study of seasonal effects on the incidence of smallpox.

Seasonal Variations in Incidence

Most infectious diseases show characteristic seasonal variations in incidence. In temperate climates, where there are pronounced seasonal differences in temperature, arbovirus infections usually occur in summer, enteroviral infections in summer and autumn, influenza and other infections of the respiratory tract mainly in winter, and measles, chickenpox and mumps mainly in winter and spring. Smallpox showed a seasonal incidence similar to that of measles and chickenpox; it was mainly a disease of winter and spring. For several of these diseases the seasonal variations are blurred in tropical climates, where the seasonal changes in temperature and humidity are often much less marked. However, smallpox showed a response to seasonal effects in many tropical regions; in Bangladesh the seasonality was so pronounced that smallpox was called, in Bengali, *guti bashunto*, the spring rash (Joarder et al., 1980).

The most detailed studies of the seasonality of smallpox were those reported by Sir Leonard Rogers, using mortality figures from British India (Rogers, 1926, 1948) and data on reported cases from England and Wales (Rogers, 1928) and certain parts of Africa (Rogers, 1948). Although many of his data were poor, comprising deaths rather than cases, both being grossly underreported, Rogers' observations of the seasonal incidence of smallpox have been confirmed by the more accurate data on case incidence obtained during the global smallpox eradication campaign.

Fig. 4.6 shows the monthly incidence of reported cases of smallpox in representative countries in the Northern and Southern Hemispheres and in the humid tropics. In Bangladesh the maximum reported incidence was in the period from January to the end of April; in Brazil, in the Southern Hemisphere, the maximum reported incidence occurred in the spring, from August to the end of October, with well-marked minima in September to the end of December and in February to the end of May. The maximum incidence in Indonesia occurred in January but thereafter the monthly incidence showed little variation. Bearing in mind the delays in reporting (see box), the maximum transmission rate probably occurred in December in Bangladesh and in June in Brazil—i.e., during the early winter. Old records for European countries (Low, 1918; Mielke et al., 1984) show that smallpox there was also mainly a winter disease.

Within India, Rogers (1928) observed that the seasonal fluctuation was the least marked and the incidence the most uniform from year to year in the State of Tamil Nadu (formerly Madras), in South India, which experienced little seasonal variation in temperature and humidity; these observations were confirmed for the city of Madras by Rao et al. (1960). Other countries in the tropics, which also

Interpreting Seasonal Fluctuations in Incidence

The analysis of seasonal factors in smallpox is based on curves of monthly incidence of reported cases or deaths, as illustrated in Fig. 4.6. The extent of reporting may affect such curves in a dramatic way, as illustrated during the "search weeks" in India (see Fig. 4.3) and after the initiation of the Intensified Smallpox Eradication Programme in Ethiopia (see Fig. 4.4). However, if it is assumed that the extent of reporting was reasonably uniform throughout each year, over a period of several years, clearly there were large differences in the incidence of reported cases at different times of the year. It is reasonable to ascribe such seasonal effects on the incidence of smallpox to factors, biological and/or social, that affect transmission. It is necessary, however, to determine the average time-lag between transmission and the recording of cases in the statistics.

As the WHO system reported smallpox cases by date of detection rather than date of occurrence, the observed pattern of disease represents a delay from actual transmission by periods of up to 2 months. Factors contributing to this time-lag include the incubation period, delays in case detection, and delays in reporting. As many outbreaks were not detected until the 2nd, 3rd or 4th generation of transmission, all cases detected on the initial investigation would have been recorded in that week—the week of detection.

experience less pronounced seasonal differences in humidity and rainfall—e.g., Indonesia and Zaire—likewise exhibited much less pronounced seasonal differences in the incidence of smallpox (Fig. 4.6). But where there were clearly distinguishable hot and cool seasons, with high and low absolute humidities respectively, the incidence was always much higher in the cool, dry season. Data on importations of smallpox into Europe during the period 1961–1973 support the findings in the endemic countries (see Chapter 23). There were 3 times as many importations during the months December–May as in the following 6 months, which is explained by the higher incidence of smallpox in the main "exporting" countries in the Indian subcontinent at that time. Further, each case imported during December–May gave rise to an average of 24 subsequent cases (median 4.5), whereas each case imported in the period June–November gave rise to an average of 1.6 cases (median 1.0) (Henderson, 1974).

A variety of factors can be envisaged that could have contributed to the seasonal incidence of smallpox: viability of the virus in an infectious state, social factors and possibly the physiological susceptibility of the host.

Viability of the virus

Experiments described in Chapter 2 show that the viability of variola and vaccinia viruses was less prolonged at high than at low temperatures and at high than at low humidities. This was true with virus in scabs (Huq, 1976), on raw cotton (MacCallum & McDonald, 1957) and in an aerosol (Harper, 1961). The correlation of low temperature and humidity with a higher incidence of smallpox was observed in many different countries—e.g., India (Rogers, 1928; Basu et al., 1979), Bangladesh (Joarder et al., 1980), western and central Africa (Foege et al., 1975), Brazil (Morris et al., 1971), the USSR (Low, 1918) and Nyasaland (Malawi) (Rogers, 1948)—suggesting that the effect of environmental conditions on the viability of variola virus was probably an important factor in determining the seasonal incidence of smallpox. In some situations, this physical effect was supplemented and amplified by social events that increased opportunities for transmission during the dry season (see below).

Changes in susceptibility of the host

Another possibility, often invoked to explain the winter incidence of influenza, is that there may be seasonal changes in individual susceptibility, due perhaps to changes in mucous membrane permeability or to alterations in resistance associated with dietary changes. There is no convincing evidence that such factors were important in smallpox.

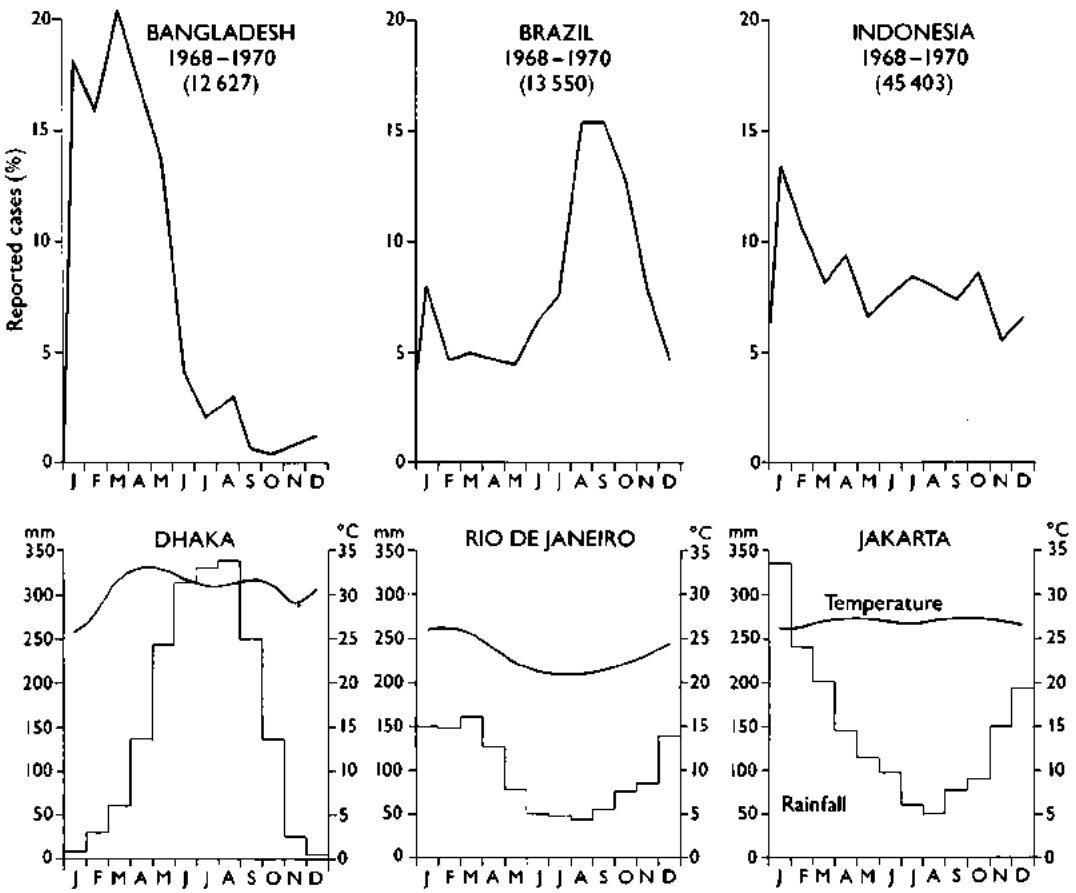

Fig. 4.6. The monthly incidence of reported cases of smallpox in countries situated in the Northern Hemisphere (Bangladesh), mainly in the Southern Hemisphere (Brazil) and in the tropics (Indonesia), as observed during the Intensified Smallpox Eradication Programme. Figures in brackets indicate numbers of cases. The lower graphs show the average monthly rainfall (mm) and maximum temperatures (°C) for Dhaka (Bangladesh), Rio de Janeiro (Brazil) and Jakarta (Indonesia). There was a pronounced seasonal incidence in countries with well-marked wet and dry seasons, but this feature was not as obvious in localities in tropical countries with sustained high humidities, such as Java (Indonesia), or Madras (India).

Social factors

Social factors of various kinds amplified the effects of temperature and humidity on the viability of variola virus. In western and central Africa, Foege et al. (1975) observed that the seasonal variation—low in the rainy season (September, October) and reaching a peak in the late dry season (March and April)—was less marked in the humid coastal areas and more pronounced in the dry savanna or Sahel. They suggested that in part, at least, this was due to the effects of climate on social activities. Planting during the rainy seasons resulted in the dispersion of the population in the fields, whereas in the dry seasons there were festivals and many more social contacts in the agricultural areas and the long-distance movement of nomads in the sub-Saharan areas. These activities facilitated the dissemination of the virus.

In Tamil Nadu (Madras), where the seasonal variation in the incidence of smallpox was not pronounced, Rao (1972) suggested that such variation as was seen was more "man-made" than natural. For example, two population groups belonging to two different communities and professions (Harijans and Gounders) lived very closely together in the same villages, but an outbreak of smallpox was limited to the Gounders (WHO/SE/68.6, Rao). Also, there was greater crowding and, because of the seasonal fluctuation in births, greater numbers of unvaccinated infants in the winter and rainy months, which Rao believed was enough to explain the limited seasonal fluctuation in incidence seen in

Forecasting Epidemic Years

The prime motive for Roger's studies was to forecast years when smallpox might cause major epidemics. Bearing in mind that seasonal conditions alone were not sufficient to produce epidemics, which could not occur if the pool of susceptible individuals was substantially reduced by recent epidemic prevalence, Rogers (1928, 1948) found a remarkably good association between failure of the monsoon rains and consequently low absolute humidity during the rainy season and epidemic prevalence in the following dry season. Transmission always continued through the rainy season, but there were more chains of transmission when the monsoon rains were poor than with a good monsoon and sustained high humidity. Thus, if the monsoon failed, the population was already extensively seeded with virus when the cooler dry season began, and the stage was set for a major epidemic. Using this criterion, Rogers (1948) found that the great majority of major epidemics could be correctly predicted; most exceptions were satisfactorily explained by the arbitrary nature of his criterion of "epidemic levels". Murthy et al. (1958) noted that in Uttar Pradesh more severe epidemics were likely if an unduly high incidence of smallpox occurred in the post-monsoon months of October and November.

Another factor, on which Rogers did not comment, was that when the monsoon rains were poor, the harvests were also poorer and hunger was more widespread. The extensive movements of refugees and others in search of food led to increased opportunities for the transmission of smallpox.

Madras city. On the other hand, in Pakistan, Mack et al. (1972b) found that there was no seasonal variation in the incidence of transmission within compounds; almost all susceptible subjects were infected when exposed to a case of smallpox, regardless of season. The interval between successive generations of cases was about 3 days longer in the cool season, a result compatible with longer viral survival but not explained by changes in social activity.

Seasonal variation in incidence in relation to eradication

Whatever its causes, the seasonal variation in the incidence of smallpox was an important factor in the planning of national eradication campaigns. For example, in India before 1973 it had been customary to utilize the end of the monsoons and the beginning of the cool season (September–October), when relatively little transmission occurred and there was no public pressure on health workers to vaccinate, as the leave period for smallpox programme workers. With the intensification of the eradication programme in 1973, rather than merely reacting to the high frequency of disease during the dry season, the policy was changed to concentrate on reducing the foci of infection during the wet season, when cases were the least numerous. In several countries, the efforts of smallpox workers during the rainy season were concentrated in the urban areas, where smallpox foci were the most numerous. When the rural areas became more accessible at the end of the wet season, efforts were made to eliminate persistent foci of infection during the seasonal lull in transmission.

INFECTION AND INFECTIVITY

Routes of Exit and Entry of Virus

The pathogenesis of smallpox, outlined in Chapter 3, is concerned in the main with how variola virions moved between different cells, organs and tissues within the human body and how the body responded. Epidemiology is concerned with the movement of virus particles between human beings—i.e., with the spread of infection in populations.

There are three principal routes of viral infection, corresponding to the three principal surfaces of the body: the respiratory tract, the alimentary tract, and the skin. Minor routes of infection include the urinary and genital tracts and the conjunctiva. Although congenital infection occasionally occurred in

smallpox (see Chapter 1), it was of no epidemiological importance and will not be discussed further in this chapter.

There is no evidence that infection ever occurred via the alimentary tract in smallpox. In experiments in monkeys, A. R. Rao (personal communication, 1981) fed concentrated suspensions of variola virus in food, or introduced concentrated viral suspensions directly into the stomach with a stomach tube. The monkeys were not infected, nor could virus be recovered from their stools. The latter result may have been due to the fact that variola virus probably behaves like vaccinia virus, which is rapidly inactivated in sewage (K. R. Dumbell, personal communication, 1982).

Mechanical transmission by arthropods is important in some poxvirus infections (myxoma virus in rabbits, fowlpox virus in birds). Sarkar et al. (1973c) showed that mosquitos could contaminate their probosces with variola virus by feeding on viraemic mice, and they speculated about the relevance of this to human smallpox. Houseflies could and probably did transport variola virus mechanically, especially in tropical countries, but their importance was probably trivial compared with other sources of infection and in any case there is no evidence that the ingestion of virus-contaminated food would produce smallpox. There is no epidemiological evidence to suggest that arthropods of any kind were involved in the transmission of smallpox.

Natural infection in smallpox usually occurred via the oropharynx or nasopharynx, sometimes via the lower respiratory tract, in special cases (inoculation variola and variolation) via the skin, and possibly, but in any case very rarely, via the conjunctiva. Before describing the processes of infection by these routes it is useful to consider how variola virions were shed from the infected patient and entered the environment and the way in which their mode of exit from the patient may have influenced their infectivity for man.

Shedding of Variola Virus

As we have shown in Chapters 1 and 3, after an incubation period of 12–14 days during which there was no evidence of viral shedding, lesions developed in the skin and the mucous membranes of the nose and mouth.

Oral, nasal and pharyngeal secretions

Because there is no tough stratum corneum in the mouth and pharynx, the lesions there ulcerated very soon after their formation (see Chapter 3, Plate 3.7) and released large amounts of virus into the oral and pharyngeal secretions. Several reports are available on the viral content of oropharyngeal secretions in variola major, all carried out with material obtained from cases occurring in the Indian subcontinent (Madras: Downie et al., 1961a; Calcutta: Sarkar et al., 1973a; Bihar: Kitamura et al., 1977b; Karachi: Shelukhina et al., 1973). Table 4.7 sets out the results of the two most extensive studies. The higher proportion of positive results recorded by Sarkar et al. (1973a) probably reflects the different modes of collection of the specimens in the two studies: throat swabs in Sarkar's series (of which the whole extract in 1 ml of fluid was assayed) and 5 ml of mouth washings (of which only 0.2 ml or 0.3 ml was assayed) in Downie's series. Besides the volumetric differences, throat swabs could be expected to detach virus particles from superficial lesions as well as including those free in the saliva. Both groups of investigators recorded positive results throughout the period of rash (3rd–14th days).

The results of titrations carried out by Sarkar et al. (1973a), shown in a condensed

T.K. GHOSH; 1983

Plate 4.2. Jaladhi Kumar Sarkar (b. 1916). Formerly Professor of Virology and Director of the School of Tropical Medicine, Calcutta, India. He carried out many investigations into the virology and epidemiology of smallpox as it occurred in Calcutta.

Table 4.7 Variola virus in the oropharyngeal secretions and urine of cases of variola major

Day of disease (from onset of fever)	Oropharyngeal secretions				Urine			
	Downie et al. (1961a)		Sarkar et al. (1973a)		Downie et al. (1965a)		Sarkar et al. (1973a)	
	Number tested	Number positive	Number tested	Number positive	Number tested	Number positive	Number tested	Number positive
1	1	0	-	-	-	-	-	-
2	4	0	2	2	-	-	-	-
3	8	4	10	10	-	-	5	5
4	20	8	22	22	-	-	9	9
5	39	18	20	20	1	0	16	15
6	49	32	22	22	3	1	14	12
7	51	33	22	21	5	3	10	6
8	39	24	18	14	4	2	9	6
9	34	22	18	11	3	2	8	6
10	10	0	13	7	4	2	5	4
11	15	4	10	6	3	2	5	4
12	12	3	8	4	5	2	3	3
13	12	1	9	4	1	1	4	4
14	5	1	5	4	2	1	-	-
15	3	0	2	0	1	0	3	3
16	1	0	1	0	1	1	1	0
17	2	0	-	-	-	-	2	1
18	4	0	-	-	-	-	1	0
19	-	-	-	-	-	-	2	1
20	-	-	-	-	-	-	1	0

Table 4.8 Variola virus in the oropharyngeal secretions of cases of variola major[a]

Day of disease (from onset of fever)	Results			Number of positive specimens with titre of:[b]					
	Number tested	Positive							
		Number	%	10	10^2	10^3	10^4	10^5	10^6
2	2	2	100	-	-	-	1	1	-
3	10	10	100	-	-	2	1	6	1
4	22	22	100	-	-	7	7	8	-
5	20	20	100	-	-	10	7	3	-
6	22	22	100	1	8	7	6	-	-
7	22	21	95	2	8	9	2	-	-
8	18	14	78	2	7	3	2	-	-
9	18	11	61	1	7	3	-	-	-
10	13	7	54	3	3	1	-	-	-
11	10	6	60	1	4	1	-	-	-
12	8	4	50	1	3	-	-	-	-
13	9	4	44	4	-	-	-	-	-
14	5	4	80	2	2	-	-	-	-
15	2	0	0	-	-	-	-	-	-
16	1	0	0	-	-	-	-	-	-

[a] Based on Sarkar et al. (1973a).
[b] Titres expressed as pock-forming units per ml.

form in Table 4.8, reflect the high viral content of the oropharyngeal secretions during the first week. The viral titres reached their highest level on the 3rd and 4th days of the disease (i.e., just after the appearance of the rash); they were highest and persisted for the longest period in the most severe cases (confluent, which in Sarkar's terminology included confluent ordinary-type and flat-type smallpox). In fatal cases virus was usually still present in the throat swabs at the time of death; in non-fatal cases it was found for as long as the 14th day from the onset of fever in confluent ordinary-type smallpox and until the 7th–9th days in discrete ordinary-type smallpox.

Skin lesions

The titres of virus in vesicular fluid and in scabs were assayed by Mitra et al. (1974) and Kitamura et al. (1977b). On about the 18th day of the disease (15th or 16th day of rash) the skin lesions scabbed and subsequently the scabs separated. Assay of the viral content of such scabs revealed that they contained a large

amount of virus and that the viral titre, as assayed by extracting the scabs in saline, remained at a high level throughout convalescence (Mitra et al., 1974).

Epidemiological observations, described below, abundantly confirmed the higher frequency of infection after face-to-face contact with a patient during the 1st week of rash. Exposure to patients in the late stages of the disease, when large amounts of virus were being released into the environment in the scabs, was much less likely to produce infection in susceptible contacts. The reasons for this difference in frequency of transmission were difficult to study experimentally. Oropharyngeal secretions expelled early and scabs released late in the disease contained virions that were equally infectious by ordinary assay methods, which involved suspending material from swabs in saline, or homogenizing the scabs by grinding, and assaying the suspension or the homogenate on the chorioallantoic membrane or in cultured cells. Perhaps the main reason for the differences observed lay in the physical state of viral particles shed by the patient from the enanthem and in scabs.

Virions released from lesions of the enanthem into the oropharyngeal secretions in the early stages of the rash were expelled by the patient in liquid droplets of various sizes, which might be inhaled by persons in close contact with the patient or transferred directly to the nose or oropharynx by fingers or objects contaminated with infected saliva or nasal secretions (Knight, 1973; Gwaltney & Hendley, 1978). Many of the large droplets would rapidly fall and dry on the bedclothes or the floor, being readily dispersed again in the immediate vicinity of the patient. Virions transferred in these ways would readily come into contact with susceptible cells. In hospitals in non-endemic countries, nurses who made up the beds of patients suffering from undiagnosed smallpox were often infected; others were protected by vaccination but developed "smallpox-handler's lung" due to the inhalation of virus.

In contrast, virions in scabs were enclosed within the inspissated pustular fluid and were present in flakes which contaminated the patient's skin and bed-linen and the dust on the bed and the floor of the room. It is likely that virions in scabs would rarely have come into direct contact with susceptible cells, since inspired particulate matter of this kind is usually swept up in the mucous secretions of the oropharynx and swallowed, or expelled again into the environment. However, such virions could retain infectivity for long periods, as judged by laboratory assay.

In spite of this virological evidence, the policy of isolating patients adopted during the Intensified Smallpox Eradication Programme followed that traditionally taught—i.e., patients were not removed from isolation in hospital or at home until the last scab had separated. As smallpox eradication became imminent in Bangladesh and India, villages were considered to house infective persons for 6 weeks after the onset of the last recognized case. This policy of isolation and surveillance provided a safety margin, since sometimes infants or other persons became infected and were hidden from surveillance officers, thus constituting a missed generation of cases.

Several studies have been made of the presence of variola virions in the air and on fabrics and skin in the vicinity of smallpox patients. In evaluating these reports it must be borne in mind that the ventilation rate of adult human beings is about 10 litres per minute, so that the air-sampling device would have had to test a volume of about 600 litres in order to be comparable to an hour's exposure of a susceptible adult person. Unfortunately, rather inefficient methods of air sampling were used in the earlier studies. Using small glass funnels tightly packed with dry cotton wool through which air was drawn, Meiklejohn et al. (1961) obtained only one positive result in the wards of the Infectious Diseases Hospital in Madras. Subsequently, Downie et al. (1965a) analysed the immediate environment of smallpox cases in the same hospital using three devices: (1) a fluid impinger which excluded particles of 18 μm or more in diameter, held near the patient's mouth for periods of 10–15 minutes that included talking and coughing; (2) settling-plates placed below air samplers; and (3) swabbing of skin and bedclothes. The results, summarized in Table 4.9, show that virus was rarely found in the small airborne droplets or droplet nuclei, although the saliva and the patient's pillow covering were heavily contaminated.

Westwood et al. (1966) studied the problem experimentally by assaying the air in the environment of rabbits infected with rabbitpox virus with sampling devices similar to those used by Downie et al. They recorded some positive results, but sampling was often negative at times when the rabbits were clearly infectious. Thomas (1970a) repeated

Table 4.9 Recovery of variola virus from the vicinity of patients with variola major[a]

Source of sample	Number of patients	Number of specimens	Positive	
			Number	%
Impinger, near mouth	29	47	5	11
Settling-plates, near mouth	13	30	12	40
Circumoral swab	32	58	42	72
Pillow swab	40	67	41	61
Impinger, near bedclothes	9	15	5	33
Settling-plates, near bedclothes	13	20	11	55
Bedclothes swab	11	16	15	94
Back swab	35	66	25	38
Urine	16	34	17	50

[a] Based on Downie et al. (1965a).

these experiments using a slit sampler (Andersen, 1958; Thomas, 1970b) that sampled a larger volume of air and did not discriminate against the collection of larger particles from a heterogeneous aerosol, as did the fluid impinger and electrostatic precipitator. As might be expected, he obtained more frequent positive results and recorded higher titres of virus than the earlier workers. Subsequently Thomas (1974) compared impingers and sedimentation plates of the type used by Downie et al. (1965a) and a slit sampler like that used in his rabbitpox experiments in the sampling of the air in a hospital in England. His subjects were a few patients in a ward who were recovering from variola minor, a situation in which much less environmental contamination with virions would have been expected than in the Infectious Diseases Hospital in Madras. The impingers gave uniformly negative results, but virus was detected with the slit sampler in air near the bed on several occasions, associated with the physical activity of patients with active lesions. Sedimentation plates exposed for some hours about 20 feet from the occupied beds also yielded virus on several occasions.

An important feature of smallpox in relation to long-distance airborne spread was that patients with uncomplicated smallpox usually had no respiratory signs or symptoms; coughing and sneezing, which generate large clouds of infective aerosols in the acute stages of measles, for example, rarely occurred. When they did, as in the index cases in the Monschau and Meschede Hospital outbreaks (Anders & Posch, 1962; Wehrle et al., 1970; see later in this chapter) airborne infection within buildings could occur.

Urine

The urine was examined for variola virus by Downie et al. (1965a) and Sarkar et al. (1973a), with the results shown in Table 4.7. Sarkar et al. recorded the titre of virus in cases which at some time had viruria (21 out of the 39 cases examined). The titre was highest early in the disease (days 5 and 6); it was higher and more persistent in severe cases (haemorrhagic smallpox and those with a confluent rash) than in milder cases. No virus was detected in the urine of some cases whose severity was comparable to that of cases with viruria. Shelukhina et al. (1973) reported that a few patients excreted small amounts of virus in the urine during convalescence (23rd and 25th days of the disease). However, both because of the small quantities of virus involved and because of the mode of excretion, it is unlikely that urine was an important source of infectious virus.

Routes of Infection

Variola virus usually gained entrance to the body via the oropharynx or respiratory tract, and occasionally through the skin, usually by direct inoculation, as practised in variolation.

Entry via the respiratory tract

Particles enter the nose or mouth, other than in food or drink, either by inhalation, or by implantation on the oral or nasal mucous membrane by contact with contaminated fingers. A great deal of experimental work has been carried out on the fate of inhaled bacteria and viruses (reviewed in *Bacteriological reviews*, 1966; Gregory & Monteith, 1967; Hers & Winkler, 1973). Some relevant aspects can be summarized as follows. The ventilation rate of an adult human being is about 10 litres per minute. Most particles larger than 15 μm in diameter and about half those 6 μm in diameter are retained in the nose. Large particles deposited in the nasal cavity or oropharynx are usually carried to the back of the throat and swallowed. Particles deposited in the lower respiratory tract may be trapped in the mucus and borne upwards from the lungs to the back of the throat by ciliary action. However, smaller particles may reach the lungs, those 1 μm or less in diameter reaching the alveoli, where they may cause

infection of cells of the alveolar walls, or alveolar macrophages.

Size and physical state are also important in determining whether expelled particles fall quickly to the ground or remain airborne for a long time. Large particles—particularly scabs—fall quickly to the ground. Smaller liquid particles dry rapidly and float for a long time in the air, thus increasing the chance that they may enter the respiratory tract. The vigorous shaking of heavily contaminated bed-linen may disperse clouds of small particles of infected "dust" in the air (Duguid & Wallace, 1948).

The other critical factor in determining the infectivity of both large- and small-particle aerosols generated by talking, coughing and sneezing is the concentration of virus in the secretions of the nose and mouth. Experiments with bacteria showed that many of the expelled particles were sterile unless the concentration of bacteria in the secretions reached 10^6 per ml or more (Duguid, 1946).

Organizations that some years ago were concerned with research on biological warfare carried out a great deal of work on respiratory infection with viruses, including orthopoxviruses; some investigations of this kind have also been conducted in other laboratories (Noble & Rich, 1969). Relevant publications on the subject deal with two systems: rabbitpox virus in rabbits (Westwood et al., 1966; Lancaster et al., 1966; Thomas, 1970a) and variola virus in monkeys (Hahon & McGavran, 1961; Noble & Rich, 1969). These experiments were described in more detail in Chapter 3; their importance in the present context is the demonstration that susceptible laboratory animals can be readily infected by aerosols of orthopoxvirions. However, neither in smallpox nor in the experimental infection of animals with orthopoxviruses has evidence of a primary lesion been found in either the oropharynx or the lower respiratory tract; it seems likely that infection could occur at any site from the nasal mucosa to the alveoli, but that no "local lesion" developed.

Inoculation through the skin

For the genus *Orthopoxvirus* as a whole, the skin is a relatively common portal of entry, usually through breaches in the surface, which may be minute. It is the usual portal of entry of ectromelia virus in mice (Fenner, 1947b), as well as the common route of infection with cowpox virus in both cows and humans, and was deliberately used for inducing vaccinia infection in man—i.e., vaccination against smallpox. Infection through the skin with variola virus occupied a special position in the history of smallpox. Accidental inoculation with variola virus occurred in certain occupational groups—e.g., among hospital personnel or mortuary attendants dealing with unrecognized smallpox. However, a much more common situation for centuries in India and China, during the 18th century in Europe, and up to recent times in some parts of Asia and Africa (see Chapters 6, 14 and 21), was the practice of variolation, or "inoculation" as it was called before the introduction of vaccination (Miller, 1957). In China a "snuff" of dust containing variola virus was originally used, but in other countries, and in China since the early 19th century, the virus was introduced into the skin.

Inoculation smallpox showed important differences in pathogenesis and symptoms from smallpox acquired by the respiratory route (see Chapters 1, 3 and 6). In the case of the former, there was always a local lesion at the inoculation site; "daughter pustules" often developed in the skin near the inoculation site; the generalized rash appeared two or three days earlier and the course of the disease was usually much less severe than in naturally transmitted smallpox. However, oropharyngeal lesions occurred as part of the generalized disease and these lesions, in particular, constituted sources of infection of contacts.

The Infectious Dose of Variola Virus

During the 1940s and 1950s substantial experimental work was undertaken to determine the number of particles of vaccinia virus needed to infect selected cells or animals by various routes of inoculation. It was found that for a highly susceptible animal or cell system, a single viable virus particle could initiate infection (Parker, 1938), although usually the ratio of particles to "takes" was much more than 1 to 1 (Sharp, 1965). In contrast, in man a relatively high concentration of vaccinia virus was needed to produce consistently successful primary vaccination takes. It was recognized that only a very small proportion of the virus in the inoculum was actually introduced into the epithelium by scarification or multiple puncture vacci-

nation. However, in assays by scarification, the 50% infectious dose was found to be 3×10^5 pock-forming units per ml for the Lister strain (Cockburn et al., 1957) and about 10^7 pock-forming units per ml for the attenuated CVI strain (Cherry et al., 1977).

Man was the natural host of variola virus, and *a priori* it might be expected that a single viable virus particle, lodged in an appropriate site, could be infectious, although because of non-specific protective mechanisms a larger dose would usually be required. However, assays could obviously not be carried out and this must remain a supposition based on analogy with vaccinia virus in highly susceptible hosts.

The form in which the infectious virus was presented to susceptible cells was a more important factor than the actual viral content in determining whether virus in various excretions or secretions would cause infection. For example, when variola virions were present in fresh oropharyngeal secretions, there was a high probability that unvaccinated subjects, exposed by inhalation or direct contact, would be infected. On the other hand, much larger amounts of infectious virus (as judged by laboratory assay of scab extracts) enclosed within inspissated pus in scabs usually failed to produce infection. Such fragments were handled as foreign bodies by the mucociliary cleansing apparatus of the respiratory tract and excreted or swallowed, without causing infection.

The Incubation Period of Smallpox

It was difficult to measure the incubation period accurately in situations in which smallpox was endemic, for exposure usually occurred over a period of several days. However, precise observations were possible in importations of smallpox into Europe. Downie (SE/72.3) summarized data from 16 outbreaks of variola major and 2 outbreaks of variola minor, occurring in several European countries between 1927 and 1960 and involving 898 cases. Among these the exact incubation period (from a single exposure up to the 1st day of fever) could be determined in 83 cases. Mack (1972) investigated 49 importations of smallpox into Europe over the period 1950–1971 and published histograms of the incubation periods (to the onset of symptoms) for individuals whose possible exposures extended over 1, 2 or 3 days. Subsequent to these

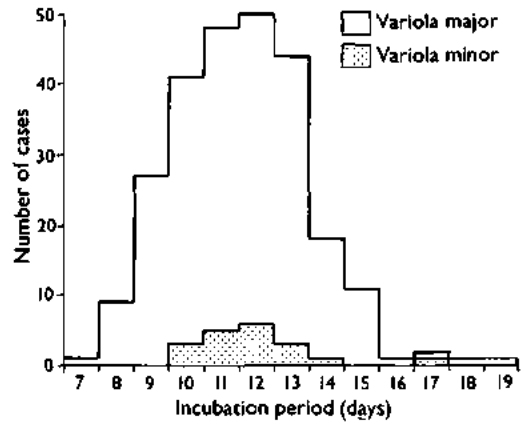

Fig. 4.7. The incubation period of variola major and variola minor, from day of exposure to the onset of symptoms. (Based on data from SE/72.3, Downie; Mack, 1972; and WHO/SE/73.57, Litvinjenko et al.)

analyses, the 1972 epidemic in Yugoslavia (WHO/SE/73.57, Litvinjenko et al.; Stojkovic et al., 1974) provided data for the calculation of the incubation period in 171 persons with variola major. Fig. 4.7 is a histogram based on the information provided by Mack for 1-day exposures in outbreaks occurring over the period 1950–1971, on Downie's data prior to 1950, and on data from the Yugoslav outbreak. In all cases the incubation period was taken as the interval between exposure and the onset of symptoms, rather than the time of appearance of the rash, which was usually 2–3 days later.

These precise data support the widely expressed opinion that the incubation period was usually 10–14 days but, in rare instances, as short as 7 or as long as 19 days. Downie concurred with the observation that acute fulminating cases of smallpox, especially haemorrhagic-type smallpox, may have had a shorter incubation period than the average, but he did not believe that previously vaccinated individuals had unusually long incubation periods, as some writers have suggested.

Variola minor appeared to have had essentially the same incubation period as variola major.

The incubation period in inoculation variola (variolation) was about 2 days shorter than in contact infection—i.e., 8 or 9 days to the onset of fever; or 5 days if the production of a local skin lesion at the inoculation site was taken as the first sign of disease (Dimsdale, 1767).

The Infectivity of Cases of Smallpox

Smallpox patients, especially those with a severe rash and enanthem, were surrounded by their infected oropharyngeal secretions and later by scabs, both of which contaminated their skin, bedclothes and to a lesser extent the air in their immediate vicinity. Susceptible individuals could be infected by coming into direct contact with the patient and his contaminated bedclothes or by inhaling infective droplets; or, more distantly, laundry workers could sometimes be infected after handling contaminated bed-linen. Very rarely, longer-range airborne infection occurred, when the contaminated droplets originating in the mouth and pharynx were smaller and more numerous, because the patient coughed or sneezed, and air currents transported infective droplet nuclei away from the immediate vicinity of the patient.

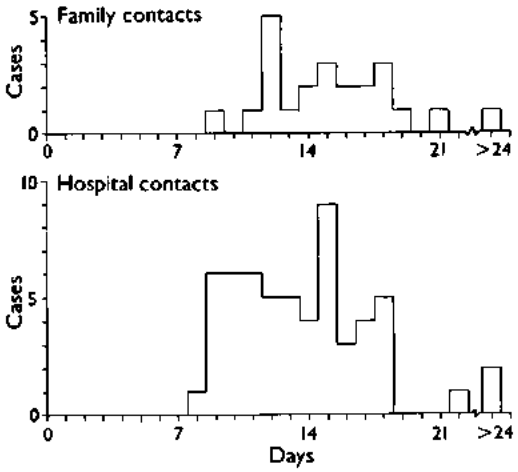

Fig. 4.8. The interval between the first possible exposure to a case of smallpox imported into Europe by air and the onset of symptoms in first generation indigenous cases, in family and hospital environments. (Based on Mack, 1972.)

Period of infectivity

The maximum infectivity of cases of smallpox was during the 1st week of rash, corresponding to the period when the lesions of the enanthem had ulcerated and were releasing virus into the secretions of the mouth and pharynx (see Table 4.8). At this stage the skin lesions were intact; the large amounts of virus later shed from the skin were not highly infectious because of the physical state of the virus particles, enclosed within hard dry scabs. For example, Mack (1972) found that the vast majority of cases infected after contact with cases of smallpox who had arrived in Europe from endemic countries while incubating the disease occurred within 3 weeks of the initial time of exposure (Fig. 4.8). In the hospital environment, the mean interval between the point at which a case first became infectious and the onset of symptoms in contacts was in the same range as estimates of the incubation period. In households, transmission took place a few days later, but in both situations the great majority of cases appeared within 3 weeks of the initial exposure.

It was difficult to obtain evidence of the infectivity of patients during the latter part of the incubation period or during the pre-eruptive fever; one series of assays of the oropharyngeal secretions of case contacts (see below) suggested that occasionally virus was present before the eruptive stage. However, epidemiological experience suggested that transmission very rarely occurred before the 1st day of rash. For example, in rural Pakistan Mack et al. (1972b) found no evidence of significant transmission during the prodromal period. Theoretically, cases remained infectious until the last scab had separated (usually from the soles of the feet) but the level of infectivity fell off greatly as the lesions of the enanthem healed during the latter part of the 2nd week of the disease.

The relative infectivity of different clinical types of smallpox

Two distinct variables were involved in determining the relative infectiousness of different cases of smallpox: the quantity of virus excreted in the oropharyngeal secretions and the number and extent of the face-to-face contacts between the patient and susceptible persons, especially during the period when large quantities of virus were being excreted. Cases with a severe rash and enanthem were more infectious than those with a slight rash and enanthem, which was why most cases of modified-type smallpox were not highly infectious. However, cases with early severe toxaemia—that is, most cases of variola major in unvaccinated persons—were usually confined to bed during the prodromal stage and were thus segregated from the community. On the other hand, although patients with modified-type variola major excreted less virus, they often moved about the community relatively freely and were thus in contact with

Table 4.10 Frequency of transmission of smallpox to household contacts in villages in Pakistan by cases occurring in unvaccinated and vaccinated subjects[a]

Status of index case	All contacts			Vaccinated contacts		
	Number	Contracted smallpox	%	Number	Contracted smallpox	%
Unvaccinated	390	83	21.3	271	15	5.5
Vaccinated	52	3	5.8	48	1	2.1

[a] Based on Heiner et al. (1971b).

many more persons. Such cases were frequently blamed for importations into the United Kingdom in the period after the Second World War, and in the 1972 outbreak in Yugoslavia 2 mild ambulant cases, not recognized as smallpox, generated 11 and 16 secondary cases respectively (Stojkovic et al., 1974). In general, however, persons who were infected despite previous vaccination were only one-fourth as likely as unvaccinated cases to transmit infection to household contacts (Table 4.10).

Rao (1972) found that the most highly infectious cases in Madras were those of ordinary- and flat-type smallpox in unvaccinated subjects. Studies in rural Bangladesh (Thomas et al., 1971b) showed that patients who died had been more infectious to family contacts during their illness than those who survived, and in rural Pakistan Mack et al. (1972b) found that while almost all susceptible persons within the relatively confined environment of compounds were infected, regardless of the severity of the index case, spread between compounds was much greater if the index case was severe.

Because the toxaemia was so much less in variola minor, cases often remained ambulatory during their period of highest infectivity and were thus likely to spread smallpox in the community, a feature which partially explains the persistence of endemic variola minor in Brazil, Great Britain and the USA after variola major had been eliminated from those countries.

Absence of recurrent infectivity

Another important epidemiological feature of smallpox was that recovery from an acute attack was followed by elimination of the virus; recurrence, with excretion of virus, never occurred (see Chapter 3). The epidemiological importance of this aspect of the pathogenesis, in relation to eradication of the disease, can be judged by comparing this situation with the recurrent infectivity found in varicella-zoster and herpes simplex infections, which accounts for the survival of these diseases in remote and isolated populations (Black et al., 1974).

The Infectivity of Case Contacts not Exhibiting Disease

Epidemiological observations before and during the eradication programme gave rise to a widely held belief that subclinical cases, patients still incubating the disease, and contacts of cases did not constitute important sources of infection. Although infection was sometimes associated with handling inanimate objects (fomites) and, rarely, seemed to be airborne over a considerable distance (see below), the vast majority of cases of smallpox could be traced to face-to-face contact of a susceptible person with a patient with overt disease, usually during the 1st week of rash. However, careful laboratory studies by Sarkar et al. (1973b, 1974) showed that about 10% of household contacts of cases of smallpox harboured detectable amounts of variola virus in their oropharyngeal secretions. Only about 10% of such carriers subsequently developed smallpox. These authors cautioned against too ready an acceptance of the view that asymptomatic carriers were not a significant factor in the epidemiology of smallpox.

Looking at the situation after smallpox has been eradicated, it seems probable that infection might occasionally have occurred from case contacts or those incubating the disease. Such events might have been responsible for what appeared to be abnormally long or short incubation periods. Nevertheless, the opinion of epidemiologists engaged in the global eradication campaign is that the vast majority of cases could be traced to close contact with a patient with an overt smallpox rash; had it been otherwise eradication of the disease from populous countries such as Bangladesh and India would have been much more difficult than proved to be the case.

Use of the Word "Contact" in Epidemiology

To clarify the discussion which follows it is useful to review the definitions used by epidemiologists for infection via the oropharynx or respiratory tract. Different conventions exist in different countries. In some countries the word "contact" is used only where true physical contact has occurred. In most English-speaking countries the word is used more broadly (Langmuir, 1973), and this was the common usage by epidemiologists engaged in the Intensified Smallpox Eradication Programme. According to this convention, infection which occurs only or mainly at short range, owing to the implantation of infectious droplets expelled from the mouth or nose of the patient during talking, coughing or sneezing, is said to occur by contact, even though physical contact does not occur. Thus "contact" includes physical contact either direct or via the fingers, as well as the direct implantation of large-particle aerosols on the oral, nasal or pharyngeal mucosae or the inhalation of small particles into the alveoli, as long as the infector and infected are in face-to-face contact.

If infection occurs at longer ranges, between persons not in sight of each other, it is regarded as being caused by airborne "droplet nuclei"—the dried particles that result from the evaporation of water from droplets that remain suspended in the air for a period. This is called "airborne infection".

However, the most common use of the word "contact" in this book is to signify a person who has been exposed to the risk of infection with smallpox, whether as a member of a household with an infected case, as a casual visitor to a hospital ward or as a co-traveller in an aeroplane, bus or train.

TRANSMISSION

The shedding of virus from an infected subject and its transfer to a susceptible person together constitute the transmission of smallpox. Transmission was ordinarily direct, by the implantation of infective droplets on to the nasal, oral or pharyngeal mucous membrane, or the alveoli of the lung, or less commonly indirect, as an airborne infection or from fomites.

Contact Infection

Contact infection could result from the inhalation of either large-particle aerosol droplets or droplet nuclei at close range or from transfer via the fingers or various objects.

Epidemiologically, the important question was the relative frequency of infection of very close contacts of the patient and infection, by aerosol, at short distances, such as occurs in tuberculosis (e.g., schoolroom epidemics) and influenza. Comparison of the intrafamilial and extrafamilial spread of smallpox (e.g., Rao et al., 1968a; Thomas et al., 1971a,b, 1972) demonstrated that the overwhelming majority of secondary infections occurred in close family contacts of overt cases of smallpox, especially in those who slept in the same room or the same bed. Next in frequency were those who lived in the same house; residents of other houses, even in the same compound (who would often have visited the house of the patient), were much less likely to become infected.

Negative evidence was also important. Especially in India, long-distance movements by train or bus of patients suffering from smallpox, with an overt rash, used to occur frequently, yet infection of casual fellow-travellers was rare indeed—so rare that instances of it were deemed worthy of special report (e.g., WHO/SE/72.41, Suleimanov & Mandokhel).

Indirect Transmission

Rather than being propelled direct from the patient on to the oropharynx or nasal mucosa of a susceptible contact or transferred by contaminated fingers or various objects (contact infection), infective particles may reach the same sites by indirect routes, after travelling considerable distances either in the

air or on fomites. Because experience had shown that most patients had been infected by face-to-face contact, indirect transmission was implicated only after all possibilities of such contacts had been eliminated.

Airborne infection

There is good epidemiological evidence that some viral infections, usually those associated with coughing and sneezing, are spread by aerosol over short distances (Coxsackievirus disease: Couch et al., 1970; influenza), while a few, notably foot-and-mouth disease, may be spread by the wind over distances of several kilometres (Donaldson, 1979; Gloster et al., 1982). Towards the end of the 19th century there was a great controversy in Great Britain about the siting of smallpox hospitals, based on the view propounded by some (e.g., Power, 1886; Buchanan, 1905) that infection could be carried by aerial spread for considerable distances from such hospitals. Collie (1912) and Dixon (1962), in reviewing the evidence, pointed out the difficulty of proving the occurrence of this type of spread in situations in which smallpox was endemic or not under control; mechanisms other than aerial spread could have been responsible in most instances. However, Christie (1980) describes a particular case which he claims is best explained by aerial spread from a hospital situated 400 yards (about 365 metres) away.

In India also it was sometimes said that the hospital was the focus from which the wind-borne spread of smallpox occurred. Hospitals were usually located in densely populated areas inhabited by persons of low income, whose vaccination status was often poor. Careful investigation showed that outbreaks of smallpox in these communities were associated with importations from outside the area—e.g., from distant construction sites—and not with spread from the hospital. In Madras, A. R. Rao (personal communication, 1981) noted that the hospital was surrounded by a zone relatively free of smallpox, probably because of more efficient vaccination in that locality. Further, Rao (1972) noted that, although wards for infectious diseases other than smallpox and corridors used by patients with such diseases were located within a few feet of the smallpox wards of the Madras Infectious Diseases Hospital, only 7 cases of smallpox presumably infected in the hospital occurred among 130 000 non-smallpox patients over the 10 years 1959–1968.

Nevertheless, airborne infection over short distances did sometimes occur. Two hospital outbreaks in the Federal Republic of Germany, at Monschau (Anders & Posch, 1962) and Meschede (Wehrle et al., 1970), seem certainly to have been airborne. In the Meschede outbreak an electrician who had just flown back to the Federal Republic of Germany from Karachi, Pakistan, and who, it transpired, had never been successfully vaccinated, was admitted 10 days later to the isolation ward of a large general hospital with a feverish illness that was suspected to be typhoid fever. He was confined to his room, and 3 days after admission developed a rash. Smallpox was confirmed by electron microscopy 2 days later and the patient was then transferred to the smallpox hospital. In spite of rigorous isolation of the patient (because of the suspicion of typhoid fever) and, after smallpox was suspected, the vaccination of all patients and nurses in the general hospital (in several cases with inactivated vaccine), or inoculation with vaccinia-immune globulin, 19 further cases of smallpox occurred there, on all three floors of the building in which the index case had been nursed. The dates of onset of these cases are shown in Fig. 4.9A. Seventeen cases occurred within one incubation period, counting from the 3 days during which the index case was in the hospital and infectious; the last 2 were room contacts of earlier cases, as indicated. The locations of these patients within the hospital are given in Fig. 4.9B, which also shows the results of tests on the carriage of smoke through the hospital. A number of circumstances favoured the airborne transmission of variola virus in this episode:

(1) the index patient had a densely confluent rash and severe bronchitis and cough;

(2) the relative humidity in the hospital was very low, a situation that promotes the survival of vaccinia virus (Harper, 1961) and presumably therefore of variola virus; and

(3) the design of the hospital led to the raising of strong air currents when the building was heated, as it was during the winter, when the episode occurred.

A visitor to the hospital during the period in question (Case No. 8) spent only 15 minutes inside the hospital, away from the patient care areas and the isolation unit corridor, but he nevertheless developed smallpox with onset of fever 11 days after this visit. Case No. 15 was a nurse who was located on the top floor;

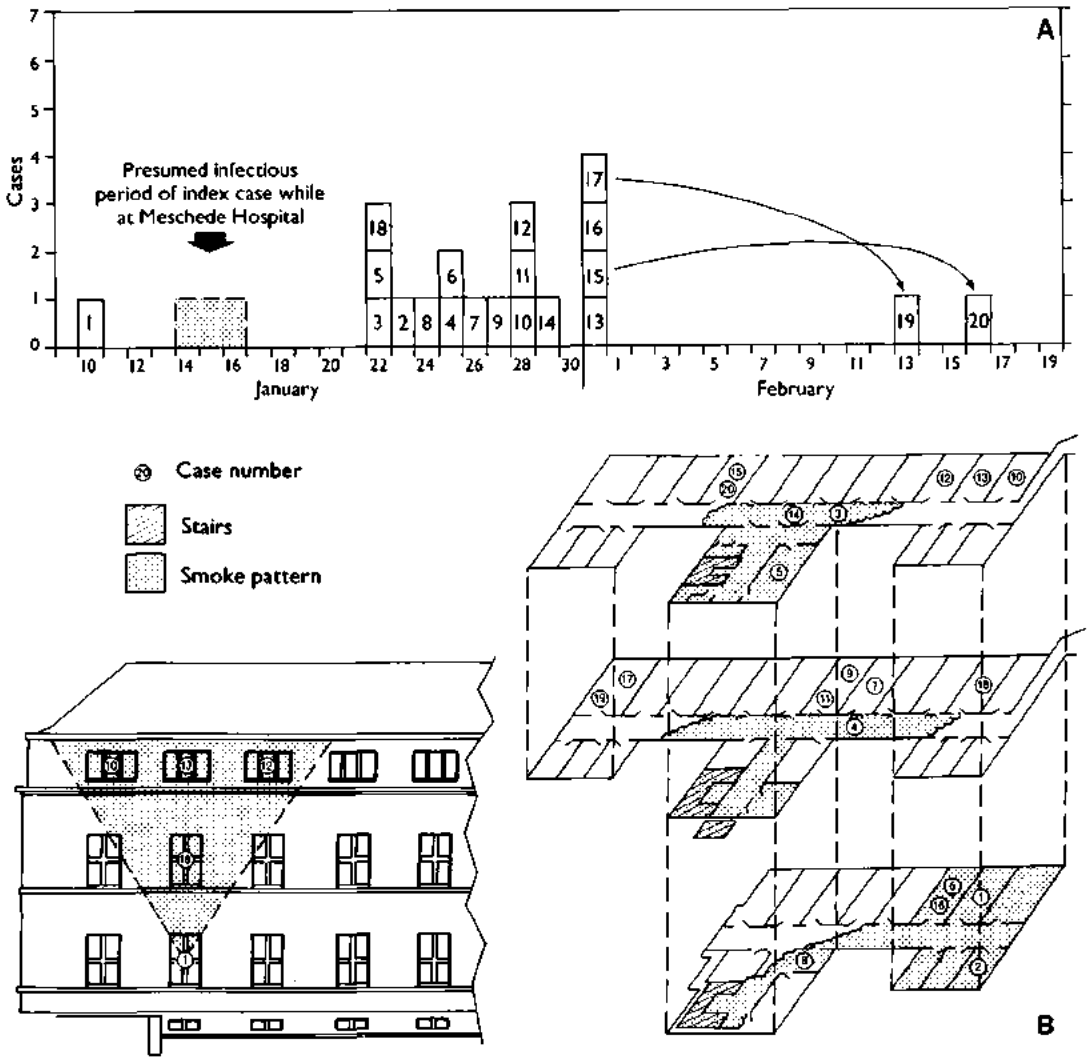

Fig. 4.9. Airborne spread of smallpox in the Meschede Hospital, Federal Republic of Germany, in 1970. **A**: Sequence of infections. The numbers in the histogram indicate case numbers, representing patients who were located as shown below. No. 1 was the index case, No. 8 was a visitor who had spent no more than 15 minutes in a ground-floor office, and No. 19 and 20 were second generation cases who had been in contact with No. 17 and 15 respectively. **B**: Floor plan and rear elevation of the hospital building, showing the location of all cases of smallpox. The shaded area indicates the movement of a cloud of smoke generated in the room in which the patient who was the index case (No. 1) had been nursed before being recognized as having smallpox. (Based on Wehrle et al., 1970.)

she had not left her sick-room while the index case was in hospital nor had she been in contact with persons other than those involved with her case, but she contracted the disease, which manifested itself after an incubation period of about 16 days. Case No. 20 was infected after contact with this patient.

There is no reason to doubt that airborne infection, sometimes over considerable distances, did occur, but it appears to have been very rare. Short-range aerosol infection was probably responsible for most non-familial cases apparently infected in hospitals, buses and trains. Many laboratory manipulations, such as blending, centrifugation and pipetting, can generate substantial clouds of aerosols; airborne infection from a laboratory is suspected to have been the cause of the last outbreak of smallpox in the world, in Birmingham, England, in August–September 1978 (Shooter, 1980; see Chapter 23).

Infection via fomites

The clothing and bed-linen of cases of smallpox were heavily contaminated with virus derived from oropharyngeal secretions and later from ulcerated pustules or scabs (see Table 4.9). Such objects sometimes served as a secondary source of infectious virus for case contacts. There are several documented instances of the infection of laundry personnel whose work-places were located at some distance from the homes or hospitals in which smallpox patients had been nursed, and of chambermaids in hotels (Stallybrass, 1931). Dixon (1962) has summarized reports on infection via fomites and commented that for laundry workers the risk of infection was greatest among those who sorted the incoming laundry and could thus inhale contaminated dust; once wetted the garments and bed-linen were not infectious.

Rao (WHO/SE/72.40) carried out experiments on the persistence of infectivity of variola virus on various objects that had been deliberately contaminated. The most important finding was that, in Madras, virus on such objects was rapidly inactivated, even when they were heavily contaminated; he concluded that fomites were of little importance in the transmission of smallpox in India. In temperate climates virus in scabs could survive on fomites such as cotton for long periods of time (MacCallum & McDonald, 1957); however, virus in scabs rarely appears to have been a source of infection.

As might be expected, the corpse of a fatal case of smallpox and the associated clothing remained heavily contaminated, and smallpox sometimes occurred as an occupational disease among pathologists and mortuary attendants, particularly from unrecognized cases of haemorrhagic smallpox (Dixon, 1962). In endemic countries cases were sometimes associated with funerals (Hopkins et al., 1971c), but these could have been due to exposure by contact with unrecognized cases as often as to infection from the corpse or clothing. From time to time other fomites, such as letters, have been suspected, but incriminating evidence was hard to obtain and the subject is of historical interest only; Dixon (1962) provides a summary.

Another purported association of smallpox with infection from inanimate objects is mentioned only to be dismissed. This relates to folklore in several parts of Africa and India which held that European missionaries who occupied a house in which smallpox had occurred months or years before sometimes contracted the disease, supposedly because of residence in that house. However, in such endemic areas there were always opportunities for infection by contact with active cases of smallpox. During the Intensified Smallpox Eradication Programme repeated efforts were made to investigate such stories, but no instances were found in which infection appeared to have been caused by residence in a "contaminated" house.

c. 1970

Plate 4.3. Cyril W. Dixon (b. 1912). Worked in the Department of Preventive Medicine at the University of Leeds, England, in 1947–1959, and was Professor of Preventive and Social Medicine at the University of Otago, New Zealand, from 1959 to 1977. He was the author of the standard textbook on smallpox in the English language, which was published in 1962.

FACTORS AFFECTING THE SPREAD OF SMALLPOX

Individual Susceptibility

In the absence of immunity due to vaccination or other prior infection with an orthopoxvirus, human beings appeared to be uni-

versally susceptible to infection with variola virus. By far the most important factor affecting individual susceptibility was the immunity provided by vaccination. Individual susceptibility to the effects of infection in unvaccinated subjects was influenced by genetic factors and physiological factors such as age and pregnancy. The risk and severity of exposure was influenced by certain occupational factors.

Genetic factors

Although racial differences in susceptibility probably did exist, they were never convincingly demonstrated. Inhabitants of India, a country subject to endemic variola major for some two thousand years, remained highly susceptible to the effects of the virus, case-fatality rates of over 20% among unvaccinated individuals being common right up to the time of eradication. However, it is impossible to read the accounts of smallpox among the indigenous inhabitants of the Americas (North America: Stearn & Stearn, 1945; Mexico: Crosby, 1967; Peru: Hemming, 1970; Brazil: Hemming, 1978) without suspecting that the Amerindians, an unexposed population when smallpox was first introduced into the Americas, were more susceptible than unvaccinated whites or Negroes. When variola minor was introduced into New Zealand in 1913 from the USA, there were 114 reported cases among Europeans, with no deaths, and 1778 reported cases among the local Polynesians (Maoris), with 55 deaths (Dixon, 1962). People of the Maori race had never before been exposed to smallpox.

It seems likely that a disease as lethal as smallpox must have exerted some selection for more resistant genotypes within populations in which it had been endemic for centuries. Such selection was readily demonstrated among European rabbits exposed to the poxvirus disease myxomatosis in as short a period as 10 years (Fenner & Ratcliffe, 1965), but this was initially a much more lethal disease and it was possible to test rabbits experimentally to determine their genetic resistance. As noted in Chapter 3, the only tests of genetic susceptibility that were conducted in man related to the possibility that deaths due to smallpox had some effect on the present-day distribution of genes of the ABO blood group system. The results reported were unconvincing but do not exclude the possibility that the selection of more resistant genotypes had indeed occurred in countries such as India. The linkage between cytotoxic T-cell activity, which is important in the process of recovery from orthopoxvirus infections, and the major histocompatibility antigens (HLA in man) suggests that the latter may have been important in influencing resistance to smallpox (Chapter 3). However, very few relevant studies were carried out and no definitive data were ever obtained.

Age

The age incidence of smallpox depended mainly on the acquired immunity of the exposed population, whether due to vaccination, variolation or prior natural infection. In the absence of protective immunization, the age incidence reflected the level of endemicity. Thus, when populations were first exposed to smallpox, persons of all ages and both sexes were affected. However, if smallpox was endemic, as in the larger cities of Europe in the 17th and 18th centuries and in modern India, it was mainly a disease of childhood. On the other hand it was less explicitly a children's disease than measles or even chickenpox. In the Intensified Smallpox Eradication Programme it was found that more than one-quarter of the cases occurred among the adult population, even in India (see Table 4.2) and Bangladesh (Chapter 16, Table 16.17).

Rural areas and small villages often escaped infection for several years, and when the disease was introduced it usually affected most of the large proportion of susceptible persons that had accumulated, thus causing much greater devastation in terms of economic disruption than was the case in places in which the disease was always present.

Apart from special physiological factors such as pregnancy (see below), and in the absence of immunizing infections with either variola virus or a related orthopoxvirus (e.g., vaccinia or cowpox), the severity of smallpox, as indicated by the case-fatality rate, was greatest in the very young and the elderly (see Tables 4.2–4.5). The great susceptibility of the very young is shown in all series of figures; it was more difficult to obtain clear-cut evidence of the level of resistance in elderly persons because of the opportunity that they had of being vaccinated or of becoming infected with variola virus earlier in life. What is clear from all data is that case-fatality

rates in the age group 5–14 years were much lower than in any other age group.

Physiological factors

Apart from severe immunological deficiency states (see Chapter 3, Fig. 3.8), which, for most of history everywhere and in the countries in which smallpox had been endemic after 1967, would usually have led to death from infection during infancy or early childhood, pregnancy was the physiological state associated with the highest susceptibility to severe disease and death. Rao's data (Rao, 1972), summarized in Chapter 1, illustrate well the severity of smallpox in pregnant women; other investigators report similar findings (e.g., Dixon, 1948).

It is difficult to obtain data on the effects of nutritional deficiencies on the severity of smallpox, apart from the suggestion (Dixon 1962) that blindness due to smallpox occurred most frequently in ill-nourished subjects. Epidemiologists working in India during the eradication campaign formed the impression that cases of smallpox were more severe and deaths more frequent among ill-nourished villagers and refugees than in better-nourished subjects, but no reports have been published which document a relationship between malnutrition and smallpox comparable to that claimed for measles (Gordon, 1976).

Occupational risk

Occupational risk was related directly to the possibility of unvaccinated or inadequately vaccinated persons coming into close contact with cases of smallpox. In Europe and the USA in the period since the Second World War, nurses in particular, and doctors to a lesser extent, were often inadequately vaccinated, although they could be exposed to massive doses of virus when treating imported cases, especially cases of unrecognized haemorrhagic smallpox. Perhaps because of the effects of large doses of virus, the case-fatality rate in nurses exposed to imported cases was sometimes very high.

Social Factors

The spread of smallpox in a community depended not only on the biological factors just elaborated, the excretion of virus and the infectiousness of cases, the mode of transmission and individual susceptibility, but also on a variety of social factors that affected the opportunities for susceptible persons to come into close contact with sources of infection, primarily overt cases of smallpox. These varied from one society to another. In many countries with well-marked dry and rainy seasons, the population was much less mobile during the rainy season, and smallpox was more confined. In the dry season, travel to markets, religious festivals, fairs and similar gatherings enhanced the opportunities for the widespread seeding of cases into previously unaffected communities. Another factor, prevalent in Indonesia, was the habit of exhibiting children infected with smallpox and taking them on visits to relatives (see Chapter 13).

In contrast to diseases such as leprosy, syphilis and gonorrhoea, no social stigma was attached to smallpox, which lessened the tendency to conceal cases. Nevertheless, in a number of communities in India and in parts of Africa, cases were hidden from the public health authorities because families distrusted the local infectious disease hospitals, or because religious beliefs generated opposition to vaccination, which would have been administered to family contacts if a case had been discovered. Such concealment caused some of the most persistent outbreaks in regions otherwise free of smallpox—e.g., the Faith Tabernacle outbreak in Nigeria (WHO/SE/68.3, Thompson & Foege), and the outbreak among the Mazezuru people in Botswana (WHO/SE/74.69, Presthus & Sibiya; see Chapter 20). During national eradication programmes, cases were sometimes concealed by both local and national health service staff, the former because they feared reprimands based on accusations of inadequate vaccination and the latter for reasons of national pride. The reward system did much to minimize concealment by local health staff.

Demographic Factors

The size and density of the population at risk affected the chances of contact between susceptible and infectious persons, and thereby the extent and rapidity of the spread of smallpox. These factors have been better analysed with measles than with smallpox, but the same principles hold for both diseases, although the transmission of measles is more

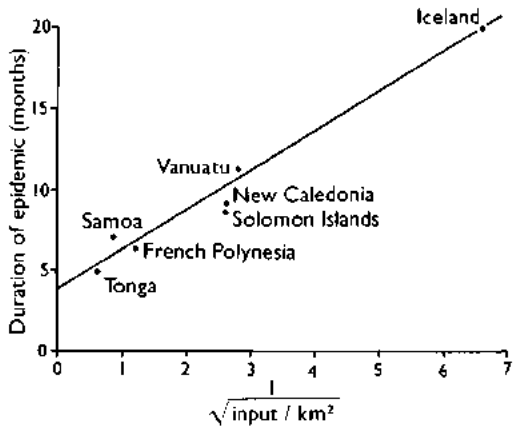

Fig. 4.10. Relationship between population density and the duration of epidemics of measles. The average distance, in kilometres, between newborn infants added to the respective populations each year is given in terms of the inverse square root of the number of new susceptible individuals added to the population per square kilometre. In island populations of roughly comparable size, the duration of epidemics was inversely proportional to the density of the population. (From Black, 1966.)

Table 4.11 Effects of population density on the numbers of unvaccinated persons remaining per unit area (km²), at various levels of vaccination coverage[a]

Persons per km²	Number of unvaccinated persons remaining when vaccination coverage is:				
	20%	40%	80%	90%	95%
500	400	300	100	50	25
300	240	180	60	30	15
100	80	60	20	10	5
25	20	15	5	3[a]	2[a]
10	8	6	2	1	1[a]

[a] Rounded to nearest integer.

efficient and rapid than was the spread of smallpox. Black (1966) has shown that in populations of about the same size, measles spread more rapidly and outbreaks terminated sooner in areas of greater population density (Fig. 4.10).

During the smallpox eradication campaigns WHO epidemiologists found that population density, when translated into the density of the susceptible population—i.e., the number of unvaccinated persons per square kilometre—was a useful concept for assessing the difficulty of controlling smallpox by mass vaccination in different endemic countries or different regions within a country (Arita et al., 1986). The effects of population density on the number and density of unvaccinated persons remaining after vaccination coverage at various levels is shown in Table 4.11. It is clear that a vaccination coverage of 80%, which was once recommended by WHO as being adequate to interrupt the transmission of smallpox, may leave a population density of 100 unvaccinated subjects per square kilometre or more in countries with a high population density, such as Bangladesh. This is very much higher than the overall country-wide population density of any African country. Arita et al. (1986) provide an example. In 1967 there was a vaccination coverage of 80.8% in the Matlab Thana, an area of about 194 square kilometres in Bangladesh. The population density was 582 per km², so that the density of unvaccinated persons was 112 per km². In that year 119 cases of smallpox were reported (and probably many more occurred). This is not surprising; it would be highly unlikely that smallpox could have been eradicated from Nigeria (population density 54 per km²) or the Philippines (population density 116 per km²), for example, with no vaccination at all. Clearly, mass vaccination alone was doomed to failure in countries with high population densities; control could only be achieved when it was supplemented by a vigorous campaign of surveillance and containment (see Chapter 10). Even in countries with low population densities, surveillance and containment greatly accelerated the achievement of eradication.

The age structure of the population affected the average severity (and case-fatality rate) of smallpox, since the very young, the elderly and pregnant women had particularly high case-fatality rates. Males aged between 5 and 20 years were important in extrafamilial spread, since they moved between family groups more frequently and readily than other segments of the population and often sustained relatively mild infections, so that they were important both as "exporters" and "importers" of the disease into previously unaffected family groups. The destruction of whole tribes that occurred when smallpox was first introduced into the populations of Amerindians in the Americas and Hottentots in South Africa (see Chapter 5) was due to a combination of the lethal effects of the disease itself in what were immunologically and genetically "naive" populations, and the

social disruption and famine that accompanied the simultaneous illness of many adults of active age, as well as persons in other age groups, in these subsistence societies.

Political and Economic Factors

The level of economic development of communities generally determines the level of health services (Fig. 4.11). The higher the level of economic development, the more effectively did surveillance and containment principles apply and the earlier was variola major, in particular, eliminated from the country (see Chapter 8).

Variola minor posed an unusual problem. Because of its low case-fatality rate compared with variola major and the lack of sequelae (facial pockmarks), it had long been tolerated as an endemic disease even in affluent countries such as the United Kingdom and the USA. In poor developing countries, such as Ethiopia, variola minor ranked very low as a national public health problem, and in the 1970s it was much more important for the rest of the world than for those countries to eliminate the disease. This justified the much larger input of international manpower and funds into the programmes in the poorer countries, in order to achieve global eradication.

Variolation and Laboratory-Associated Smallpox

Although close contact with overt cases was responsible for the vast majority of cases of smallpox, there were two other potential sources of infection: variolation and the smallpox laboratory. For many centuries and as recently as August 1976, some cases of smallpox originated from the practice of variolation (see Chapters 6, 14 and 21). Such cases of inoculation variola themselves constituted potential sources of infection for susceptible subjects in close contact with them.

Until the 1970s, laboratories in endemic countries and in countries liable to importations conducted studies in the diagnosis of smallpox and often held stocks of variola virus to assist them in this work. Laboratory procedures are associated with some risk of infection both for those working with viruses that are pathogenic for man (accidental injection, trauma) and for visitors to such laboratories, which may use procedures that generate aerosols. Of all the dangerous human pathogens, variola virus was regarded by virologists as among the safest with which to work in the laboratory, since regular vaccination and revaccination provided complete protection to the workers involved. However, administrative mistakes sometimes occurred and a few cases of laboratory-associated infection

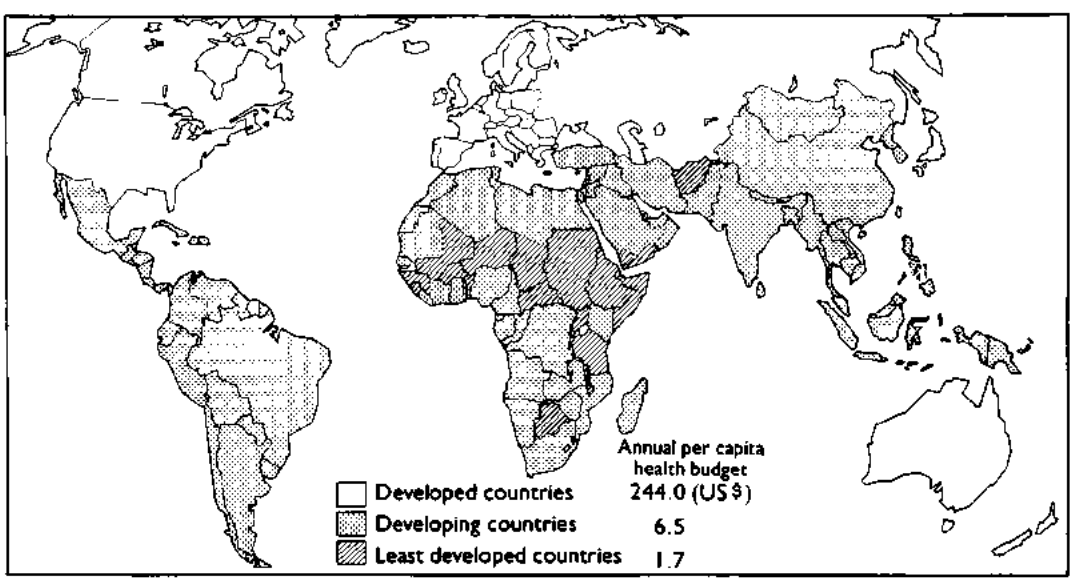

Fig. 4.11. National levels of economic development, as determined by the United Nations on the basis of average per capita income for the year 1982. Average per capita expenditures on health in US$ are also shown.

were documented in non-endemic countries. It seems likely that cases may occasionally have occurred in endemic countries also, but the source would have been more difficult to identify with certainty. The importance of the laboratory as a potential source of infection is discussed in Chapter 30.

PATTERNS OF SPREAD IN POPULATIONS

In the earlier sections of this chapter the infectivity of cases of smallpox and the susceptibility of individual human beings were discussed. The final section is concerned with various aspects of the spread of smallpox in populations, looking first at the situation in countries as a whole and then at small communities, including institutions. Several case studies are analysed which describe the epidemiology of smallpox in rural and urban settings.

Spatial Distribution

Secular trends in the occurrence of smallpox dealt with earlier in this chapter were drawn from the numbers of cases reported annually by different countries. The fact that cases were grossly and continually underreported almost everywhere meant that these figures greatly underestimated the incidence of the disease. Further, by ascribing cases to countries they fail to express the spatial distribution of smallpox. Even when smallpox was essentially uncontrolled it was never uniformly distributed within a country. An "epidemic year", for example, usually indicated a high incidence of the disease not throughout a country, but in a number of scattered villages and towns. Although smallpox remained endemic throughout the year in the large cities of endemic countries, it occurred as many small outbreaks in different suburbs and districts within the city. As the maps showing the falling incidence of smallpox in India from 1972 onwards illustrate (Basu et al., 1979), the distribution of the disease by district was patchy, and it was patchy even within affected districts.

Effective public health measures in non-endemic countries limited the spread of smallpox after importations, usually to the family and close contacts of the index case, but sometimes, as in Yugoslavia in 1972, unrecognized cases spread the disease more widely before its nature was recognized.

The Rate of Spread within Small Groups

The devastating effects of smallpox in non-immune populations in the Americas, southern Africa and the islands of the Pacific Ocean (see Chapter 5) gave rise to the view that it was one of the most infectious of all diseases. It is true that very brief exposures of susceptible persons to a case did occasionally lead to infection. For example, one case in the outbreak at Meschede, described above, was a person who had never been in face-to-face contact with a case of smallpox and had been exposed to possible airborne infection for a period of 15 minutes or less. The last person to contract endemic smallpox in the world—the unvaccinated hospital cook Ali Maow Maalin—was exposed to the disease for a few minutes only, while he directed a vehicle carrying two active cases of smallpox from the hospital in Merca, Somalia, to the home of the local smallpox surveillance team leader (Deria et al., 1980). Sometimes one index case infected a dozen or more people, as in the outbreak in Yugoslavia in 1972 (see Chapter 23). These episodes, however, were exceptional. Epidemiologists engaged in the global smallpox eradication campaign in Africa, South America and Asia agree with Dixon (1962) that smallpox usually spread rather slowly.

Attempts have been made to express quantitatively the infectiousness (or contagiousness) of different human diseases by calculating in various ways the proportion of cases among exposed contacts. The most widely used figure is the secondary attack rate—i.e., the proportion of susceptible individuals exposed to an index case within a household who became infected within the expected transmission interval of the disease. It is surprisingly difficult to obtain suitable series of data to make this calculation; often the term "secondary attack rate" has been used to include all subsequent attacks (first, second and third generation cases). Hope Simpson (1952) developed a measure that makes use of results of second and later generation attacks to provide a figure comparable to the first generation secondary attack rate—what he called the susceptible-exposure attack rate.

Some figures for measles, chickenpox and smallpox are set out in Table 4.12. The numbers available for the calculation of the

Table 4.12 First generation secondary attack rates (or the equivalent) in measles, chickenpox and smallpox

Disease and locality (for smallpox)	Vaccination scar[a]	Total number of household contacts	Contacts who developed disease		Reference
			Number	%	
Measles	..	266	201	75.6	Hope Simpson (1952)
Chickenpox	..	282	172	61.0	Hope Simpson (1952)
Chickenpox	..	888	771	86.8	Ross (1962)
Variola minor					
Brazil	–	38	20	52.6	Angulo et al. (1967)
Brazil	+	56	8	14.3	
Brazil	–	674	466	69.1	Suzart de Carvalho Filho et al. (1970)
Brazil	+	204	7	3.4	
Variola major					
Nigeria	–	27	12	44.4	Foege et al. (1975)
Nigeria	+	45	12	26.2	
Benin	–	17	8	47.0	Henderson & Yekpe (1969)
Benin	+	13	2	15.4	
Madras	–	103	38	36.9	Rao et al. (1968a)
Madras	+	1 146	14	1.2	
Pakistan	–	45	33	73.3	Heiner et al. (1971a)
Pakistan	+	190	6	3.2	
Pakistan	–	22	10	45.5	Heiner et al. (1971b)
Pakistan	+	338	3	1.3	
Pakistan	–	43	38	88.4	Mack et al. (1972a)
Pakistan	+	180	13	7.2	
Calcutta	–	80	61	76.3	Mukherjee et al. (1974)
Calcutta	+	661	47	7.1	
Bangladesh	–	21	9	42.9	Thomas et al. (1971b)
Bangladesh	+	57	4	7.0	
Average (variola major)	–			58.4	
	+			3.8	

[a] .. = not applicable; + = scar present; – = scar absent.

secondary attack rate were often quite small and the reported secondary attack rates varied widely. For variola major, the overall average secondary attack rate was 58.4% in unvaccinated family contacts, and 3.8% in vaccinated contacts. Vaccination protected most close family contacts from overt disease (but not necessarily from subclinical infection—see Heiner et al., 1971a). The highest secondary attack rates were those reported for Pakistan by Heiner et al. (1971a) and Mack et al. (1972a). These workers suggested that one of the causes of this phenomenon might have been the dry meteorological conditions prevailing for most of the year in the Punjab, compared with other parts of the Indian subcontinent. On the basis of secondary attack rates in susceptible subjects, smallpox appears to have been somewhat less infectious than either measles or chickenpox, since the figures for chickenpox exclude subclinical infections, which occur in at least 5% of varicella virus infections but are extremely rare in unvaccinated persons infected with variola virus.

This comparison of the secondary attack rates of smallpox and other common infectious diseases fails to take cognizance of an important feature of variola major, which substantially decreased the rate at which it spread outside the household. Patients in the prodromal stage of variola major, before the rash had appeared and before they could transmit infection, were usually quite ill, with toxaemia, headache and backache. Most took to bed, so segregating themselves from the general community, although not from their household contacts. In contrast, patients in the early and highly infectious stages of chickenpox and measles have few symptoms and are usually mobile, and thus spread these diseases to school and street contacts as well as to members of the household. Although its inherent transmissibility was probably lower than that of variola major, because less virus was excreted in the oropharyngeal secretions, variola minor resembled chickenpox in the mobility of infectious patients, which partly accounts for its persistence in many countries after variola major had been eliminated.

Another measure of infectiousness is the duration of outbreaks in particular community units. There are many records in the

literature of the slow spread of smallpox—for example, the outbreak of variola minor in New South Wales (Australia) in 1913–1917 (Cumpston & MacCallum, 1925; see Chapter 8) and among nomads (see below). Smallpox sometimes took several generations of infection to spread through quite small populations.

Spread in Institutions

Because of the importance of face-to-face contact in the transmission of smallpox, the household or family unit was by far the most frequently affected group. Nevertheless, some institutions, especially hospitals and schools, and public events, such as fairs and religious festivals, played an important part in the dissemination of smallpox.

Hospitals

The role of hospitals was particularly significant in amplifying outbreaks of imported smallpox, for undiagnosed and misdiagnosed cases were often admitted into general wards, and the proportion of unvaccinated or poorly vaccinated hospital personnel and patients was usually high (Millar, 1965). Over half the cases that occurred after importations of variola major into Europe between 1950 and 1971, and all the large outbreaks, were to be found among persons associated with hospitals, either occupationally or as patients or visitors (Mack, 1972). An outbreak in Glasgow in 1950 (Laidlaw & Horne, 1950) was characteristic. An Asian seaman with 4 vaccination scars and a history of revaccination 3 years earlier was admitted to hospital with what was regarded by an experienced consultant as chickenpox, but was in fact modified-type smallpox. Thirteen of the 18 cases which ensued were infected in hospital, including 10 members of the hospital staff. Six died, all of whom were unvaccinated or had failed to respond to vaccination after exposure.

The experience in the epidemic in Yugoslavia in 1972 (Stojkovic et al., 1974) was particularly dramatic: an undiagnosed case of haemorrhagic-type smallpox infected 2 contacts in a bus and then a total of 36 persons in 3 hospitals to which he was admitted.

Hospitals sometimes played a role as amplifiers in countries with endemic smallpox. Almost everywhere, they were important

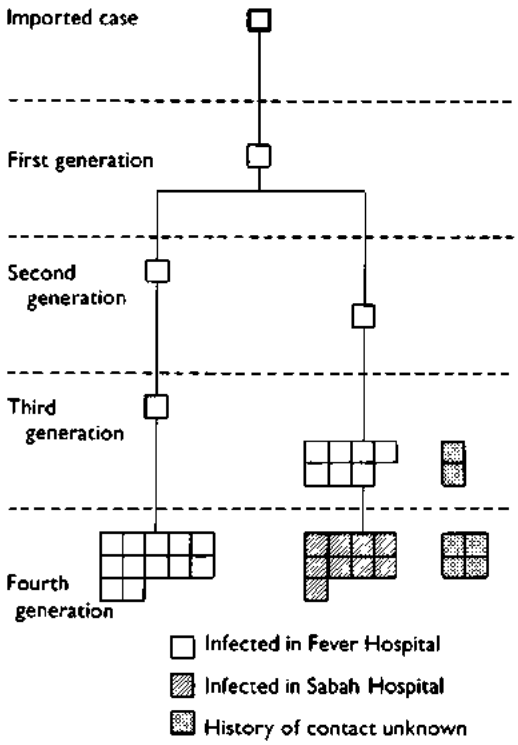

Fig. 4.12. The pattern of transmission of smallpox in an outbreak in Kuwait in which two hospitals were the principal foci of infection. (From Arita et al., 1970.)

disseminators of smallpox. Obviously, if all staff were regularly vaccinated and patients and visitors vaccinated on entry—as ideally they should have been—the risk of spread would have been very low. However, with a few exceptions, such as the Infectious Diseases Hospital in Madras (Rao, 1972), this did not occur. Two outbreaks exemplify the risk.

Kuwait is a small country which in 1967 had been free of endemic smallpox for the previous 10 years, but which was constantly exposed to the risk of importations from nearby endemic countries. Smallpox misdiagnosed as chickenpox spread in the Fever Hospital over a period of 2 months before a second generation fatal case was correctly diagnosed, after it had caused 9 third generation cases. One of these, unrecognized, was transferred to another hospital (Sabah), where it produced several more cases (Fig. 4.12). Twenty-one of the 39 cases were in children under 4 years of age; only 8 patients, 6 of them aged 15 years or more, had ever been vaccinated. In contrast to the usual situation in Europe, all cases, except one vaccine-modified attack, occurred among patients rather

than nurses or other hospital personnel, whose immune status had been maintained by regular revaccination (Arita et al., 1970).

An outbreak in a children's hospital in Brazil described by Morris et al. (1970a) demonstrates clearly the importance of the hospital as a potential focus for transmission in countries in which variola minor was endemic. The epidemic had been smouldering in the community and the hospital for at least 10 months before it was extinguished and 40 of the 51 cases that occurred in the hospital during 1967 were certainly or possibly (4 cases) hospital-associated. Over the period, there were at least 11 and possibly 15 separate introductions of smallpox into the hospital, which formed a continuous source of infection because visiting was not restricted and smallpox cases were treated in the outpatient clinic. Only one hospital employee was infected—a kitchen worker who had never been successfully vaccinated.

Schools

Because of their accessibility, schoolchildren in endemic countries were usually well vaccinated. Unvaccinated children in the infectious stages of variola major were usually too ill to attend school. Even with variola minor, contacts between children in the household or, to a lesser extent, in playgrounds appeared to have been more important than their contacts at school (Angulo et al., 1968). Space–time cluster analysis of variola minor within two schools suggested that transmission was most likely to occur from infected children to susceptible children sitting next to them (Klauber & Angulo, 1974a); studies in schools when two or three shifts of pupils occupied the same classroom each day revealed that contaminated desks or other fomites played no part in spread (Klauber & Angulo, 1974b).

In a study in Mali, Imperato (1970) found that smallpox spread much more rapidly and extensively among schoolchildren than among equally inadequately vaccinated children of the same age who did not attend school. The epidemic was confined to a group of straw buildings in which there was severe overcrowding and did not spread to children in less crowded cement-block buildings in the same school compound. However, even in the straw buildings transmission, mostly between susceptible and infected persons in close contact, was slow and went on for a long time because of the absence of an effective response by the local health personnel.

Markets, fairs and religious festivals

Markets are regular institutions at which households mingle; fairs and religious festivals, although held less frequently, draw attendance from much wider areas. Both are important as mechanisms for the wide dissemination of infectious diseases, because of the dispersion of participants during the incubation period. Great international religious festivals, such as the pilgrimage to Mecca, are kept under strict medical surveillance and appeared to have played only a minor role in the international spread of smallpox during the latter part of the 20th century, although it seems likely that some outbreaks did occur but were concealed. The national religious festivals in India were always important for the dissemination of smallpox, and in the later stages of the eradication campaign they served as convenient observation posts for sampling the vaccination status and awareness of smallpox in village populations (see Chapter 15).

On rare occasions funeral ceremonies provided an opportunity for the spread of smallpox. When death due to unrecognized smallpox occurred, relatives, friends and other associates who were obliged to attend the funeral could be exposed to a variety of sources of virus (Hopkins et al., 1971c). Like markets or fairs, funerals were important because the participants subsequently dispersed and could then produce secondary cases among widely separated family groups.

Dispersal by Travellers

Because of the long incubation period of smallpox, travellers of various kinds—migrant workers, nomads, tramps, bus and train passengers, and air travellers—could cover long distances while apparently healthy and introduce the disease into areas far removed from the place in which they had acquired the infection. The situation was dramatically illustrated by importations into European countries by air travellers (Hagelsten & Jessen, 1973; see Chapter 23), but the movement of train and bus travellers in endemic countries was no less important. Fellow-travellers

were sometimes infected when ambulant patients, perhaps with vaccine-modified smallpox, travelled in buses or trains (see, for example, WHO/SE/72.41, Suleimanov & Mandokhel). Usually the travellers became infectious after arriving at their destination, where they initiated new outbreaks. Perhaps the most dramatic of such instances of dispersal of smallpox to distant areas were those from the Jamshedpur industrial complex in Bihar, India, in 1974 (see Chapter 15, Fig. 15.20). During a 6-week period, between the end of February and mid-April 1974, travellers from Jamshedpur caused nearly 300 outbreaks in other Indian states, dispersal occurring mainly through train passengers travelling from the Tatanagar railway station. During 1974 there were many exportations from India to Nepal and in 1975 smallpox was reintroduced into India from Bangladesh on 32 occasions (see Chapter 15).

Because of their greater mobility, adult men were much more likely than women or children to acquire smallpox outside the home; the movement of sick peasants or workers from the city back to their villages appeared to be important in the maintenance of smallpox in some rural areas in the Indian subcontinent (Thomas et al., 1971a; Thomas et al., 1972; Sommer & Foster, 1974). Indeed, it was suggested that in Pakistan the cities were the reservoir of smallpox during the monsoons, the disease being carried back to the rural areas after the rains. However, when effective active surveillance was introduced, a number of affected localities were found in rural areas immediately after the monsoons, in spite of reports of "no transmission" during the rains (see Chapter 14). Not surprisingly, in countries such as India, in which 80% of the population was rural, the predominant travel pattern (74%) was from one rural area to another, and smallpox transmission followed the pattern of population movement.

Dispersal by refugees

Although they constituted a special type of traveller, refugees were of particular importance in the spread of smallpox, because of the vast numbers involved in the flight from war- and famine-stricken areas. Such dispersal was directly responsible for the re-establishment of endemic variola major in Bangladesh in 1972 (see Chapter 16). Many other instances occurred, both between and especially within countries. Movement of refugees provided almost ideal conditions for the promotion of spread—large numbers of persons of all ages living in close proximity under very unsatisfactory conditions, often suffering from malnutrition and often poorly vaccinated. The isolation of cases was difficult or impossible.

Illustrative Case Studies in Rural Areas

In the developing countries in which smallpox was most recently endemic the vast bulk of the population lives in villages in the rural areas. In India, for example, the 1971 census figures showed that 80% of the population of 548 million lived in 580 000 villages, of which 318 000 had a population of less than 500. There were only 148 towns and cities with a population of more than 100 000. In Bangladesh and in most countries of Africa the proportion of population in the rural areas was even higher. In some countries, such as Afghanistan and Somalia, some of the rural population lived a nomadic life; these nomads presented special problems in smallpox eradication programmes.

Studies in Africa

Henderson & Yekpe (1969) described the spread of smallpox in a village in southern Benin, in which about half the population of 300, as well as about half the members of the infected households, had old vaccination scars. The chronology of the epidemic and the probable chains of transmission which started with the movement of an infected woman and her children back to the village are shown in Fig. 4.13. The 3 cases infected outside the village lived in house A and the disease spread to 5 contiguous houses (B–F) by moving from one infected household to the uninfected household nearest to it. Seventeen of the 28 persons living in that cluster of houses (A–F) became ill. A 17-year-old boy living in house G, who carried food to persons in the infected cluster of households, became ill but produced no secondary cases; both his parents had vaccination scars. Infection was brought to house H by the "*grand féticheur*" (Case No. 22), whose occupation involved frequent contacts with all cases of smallpox, and he was probably responsible for the other 6 cases in the village, in houses H and I. The 2 patients in household I joined the *grand féticheur* in the funeral ceremonies of smallpox victims. Frequent casual contact occurred between the

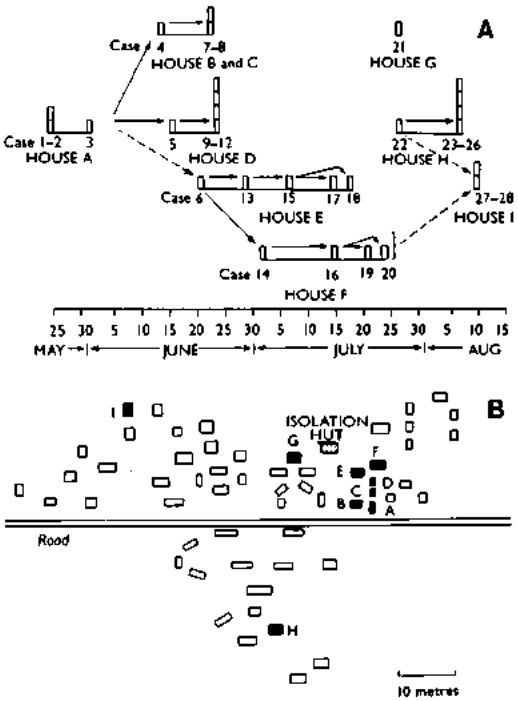

Fig. 4.13. The spread of smallpox in a village in Benin of 300 inhabitants, living in 59 houses, extending from May to the end of August 1967. **A**: Chronology and spread. Solid lines = routes of transmission; broken lines = probable routes of transmission. **B**: Location of households. (Based on Henderson & Yekpe, 1969.)

villagers in general and the smallpox sufferers, although once the rash had developed the patients were generally avoided.

The striking feature of this epidemic was the spatial localization of the disease, which reflected intimate social contact between at least some members of the affected households. Once smallpox had been introduced into a household, secondary cases occurred within it. The transmission of smallpox appeared to stop when the number of susceptible individuals in the village who were in casual contact with cases was still large but the supply of such persons in prolonged and intimate contact with cases was virtually exhausted. Even among the household contacts smallpox was not highly contagious; prolonged or intimate exposure was usually necessary. Because of this pattern of spread, it is not surprising that smallpox was eliminated from many African countries much more rapidly than had originally been anticipated (see Chapter 17).

Studies in Brazil

Similar observations emerged from a study of the spread of variola minor in a semi-rural school district in São Paulo, Brazil, in which there were two types of social agglomerates: school classes (Angulo et al., 1964) and households (Angulo et al., 1967). All the secondary cases in the 12 infected households resulted from a single introduction by a known primary case of smallpox, who was usually a child infected in the school. Infection occurred only among persons in intimate and face-to-face contact, either in the household, in the school, or in shared household facilities (Angulo et al., 1968).

Studies in the Indian subcontinent

Thomas and his colleagues have reported detailed studies of smallpox in rural areas of Pakistan and Bangladesh (see Chapters 14 and 16). Their investigations in Bangladesh (Thomas et al., 1971a, b) showed that smallpox did not remain indefinitely endemic in a rural district in which 113 000 inhabitants resided in 132 villages scattered over an area of about 200 square kilometres. During a period of 12 months, 119 cases of smallpox occurred in 30 outbreaks in 27 widely dispersed villages. Inter-village spread occurred in only one case; in the other 21 outbreaks whose source could be determined, smallpox was introduced by a landless peasant from the village in question who had contracted smallpox during a visit to a city to obtain employment. The probability of an introduction was correlated with the population size of the village, and thus with the probable numbers of landless peasants from each village seeking employment in the cities. With the introduction of smallpox into a village, secondary cases appear to have occurred more frequently outside than inside families. Nevertheless, the secondary attack rates among unvaccinated persons were highest within families.

A further, substantially larger study was carried out in Pakistan (Mack et al., 1972a, b; Thomas et al., 1972). The most striking differences between the two studies were the very high secondary attack rate (88%) among unvaccinated contacts within compounds and the high proportion of cases (78%) resulting from spread between rather than within compounds. The explanation for

the very high secondary attack rate in Pakistan is not clear; possibly it was due to the low humidity prevailing in the Punjab for most of the year. As in Bangladesh, smallpox was not maintained as an endemic disease within the rural areas, even in one as large as 6000 square kilometres with 1.2 million inhabitants. Over half the outbreaks occurring in the study area were ultimately traced to cities, emphasizing the significance in Pakistan of these large aggregations of population for the maintenance of the disease.

Investigation in Pakistan by Heiner et al. (1971b) confirmed the high secondary attack rate in the Punjab, which reached 77% in unvaccinated compound contacts and 4.8% in previously vaccinated contacts, all of the latter having been exposed to severe or fatal index cases. Further, vaccinated persons generated many fewer cases among their contacts (4%) than did unvaccinated index cases (11.5%) (see Table 4.10), reflecting the greater severity of the disease in unvaccinated subjects.

Another investigation in rural villages in Pakistan, which was mainly concerned with inapparent infections (Heiner et al., 1971a), has been discussed at length in Chapter 1. Here we would note that in this study, village residents who were not household or compound contacts of cases were taken as one of the control groups. In contrast to vaccinated compound contacts, over half of whom had had overt or inapparent smallpox, only 6.5% of these other vaccinated villagers in this control group had sustained inapparent infections (none had overt smallpox), again showing the importance of intimate face-to-face contact in the transmission of smallpox.

Prolonged transmission among nomads

Nomads constituted a special problem in the Horn of Africa, sub-Sahelian western Africa and Afghanistan. On general principles, it could be predicted that smallpox would rarely persist for long in such small isolated populations, even in the absence of control measures. This was indeed usually the case. Outbreaks among nomads constituted 68% of 843 outbreaks in Somalia in 1977, but in only 10 of them did prolonged transmission occur (Table 4.13). The best documented of these outbreaks, in Mandeelo village (Foster et al., 1978), is described in Chapter 22. As indicated in Table 4.13, transmission was interrupted very soon after outbreaks in nomads were detected, and in some instances the last case had occurred before the outbreak was detected. Similar prolonged persistence of smallpox in nomadic groups of less than 15 persons have been described in both Cameroon and Niger (Henderson & Yekpe, 1969).

This slow and prolonged transmission was due to the balance between the supply of susceptible persons and the transmission rate. Nomads were usually poorly vaccinated and patients with variola minor were often ambulant throughout their illness. The transmission rate was low because most of the activities of nomads occurred in the open, where opportunities for face-to-face transmission by large-particle aerosols were greatly reduced. As noted above, these circumstances usually led to the spontaneous termination of outbreaks (in 98.2% of outbreaks), but if transmission was maintained it continued for many weeks, even in these very small populations.

Table 4.13 Prolonged transmission of smallpox in several nomadic encampments in Somalia in 1977[a]

Locality	Population	Number of cases	Number of days from first to last case	Date of:		
				First case	Last case	Detection
Darta	55	14	163	17 Feb.	1 Aug.	20 Aug.
Oridan	35	24	152	21 Jan.	23 June	28 June
Loala	98	20	106	22 March	6 July	22 June
Bilahey	75	23	95	14 March	8 June	19 June
Madhare	35	9	80	6 March	24 May	18 May
Berdebiole	65	9	74	20 April	4 July	5 July
Boldwene	50	6	73	26 March	8 June	17 May
Abdijelib	11	6	70	25 Feb.	7 May	24 April
Mandeelo	46	21	68	23 April	1 July	23 June
Shafa	60	12	65	28 June	1 Sept.	12 Aug.

[a] The great majority of outbreaks in such groups were rapidly detected and controlled, or the chain of transmission was interrupted spontaneously. (Based on Ježek et al., 1981.)

Illustrative Case Studies in Urban Areas

Outbreaks of smallpox in non-endemic countries since 1950, most of which occurred in urban settings, are discussed in Chapter 23. Of more significance than these episodes, in relation to the global smallpox eradication programme, was the pattern of spread in urban areas in countries in which smallpox was still endemic. Only a few reports of such situations have been published, mainly referring to cities in the Indian subcontinent (Madras: Pandit et al., 1959; Rao et al., 1968a; Rao, 1972; Calcutta: Mukherjee et al., 1974; Lahore and surroundings: Ali & Heiner, 1971; Thomas et al., 1972; Bangladesh: Sommer & Foster, 1974; Brazil (variola minor): Rodrigues-da-Silva et al., 1963; Azeredo Costa & Morris, 1975).

Transmission to household contacts in some cities, e.g., Madras (Rao, 1972), showed much the same pattern as that in rural areas; transmission was usually more common among intrafamilial than extrafamilial contacts, even when all those studied lived in compounds in which families shared an entrance, toilet facilities and a bath. The importance of the local social arrangements is shown by the fact that in Calcutta Mukherjee et al. (1974) found that the attack rates among household and compound contacts were very similar; in this situation the mixing of the inhabitants was so intimate that each compound could be regarded as a single large family.

In many endemic countries the larger towns and cities constituted the major reservoir of smallpox during the wet season. Sarkar et al. (1970) studied the epidemiology of off-season cases in Calcutta in 1967 and 1968. Most of the few cases that occurred during the months June–November of each year were in beggars and footpath dwellers or in manual labourers who did not work in fixed places and lived in the bustees (slum areas). Successive cases were sometimes widely dispersed, but the majority of cases could be grouped into 6 outbreaks in the bustees, different groups being involved in 1967 and 1968. Several cases were probably associated with introductions from villages outside Calcutta, and in one instance there was evidence that infection was introduced from Calcutta into a village 30 kilometres away in May 1968, maintained there by serial transmission, and reintroduced into another part of Calcutta in September 1968.

Several reports refer to the maintenance of smallpox in small pockets of unvaccinated individuals in otherwise well-vaccinated populations. In Lahore, for example, Ali & Heiner (1971) found that in a situation in which 93% of the population had vaccination scars or a history of smallpox, the disease could persist for most of the year, mainly because of the high concentration of unvaccinated children under 3 years of age and of older persons in whom the immunity conferred by primary vaccination many years before had waned.

Experience in Indonesia (see Chapter 13) provided one of the earliest and clearest demonstrations of the ineffectiveness of mass vaccination alone as a means of eliminating smallpox from populous countries. It used to be held that a vaccination level of 80% would suffice to raise the herd immunity to such an extent that transmission would cease (see Chapter 9). However, in Indonesia in 1969 and 1970 chains of transmission of variola major were maintained in communities in which the overall vaccination rate was about 90%. This happened because of the high population density (see Table 4.11), and because a large proportion of the unvaccinated were in the age group 0–4 years. The Indonesian practice, mentioned earlier in this chapter, of taking children with smallpox on social visits to their neighbours and relatives maintained a chain of transmission in this section of the population.

Thompson & Foege (WHO/SE/68.3) demonstrated that the existence of special groups who, for social or religious reasons, refused vaccination was of significance in maintaining endemic smallpox within an otherwise well-vaccinated urban community in Nigeria. The concealment of cases played an important role in the development of the epidemic, but the disease spread quite slowly (32 recognized cases over a period of 11 weeks), even in a compound where nobody had been vaccinated. In spite of frequent social mixing on religious occasions, transmission occurred most frequently as a result of family and compound contacts. Such situations were not restricted to urban areas, for the last outbreak of smallpox in southern Africa occurred among a religious sect in Botswana, who lived in closed communities in 9 small towns and likewise refused to be vaccinated (Presthus, 1974; WHO/SE/74.69, Presthus & Sibiya).

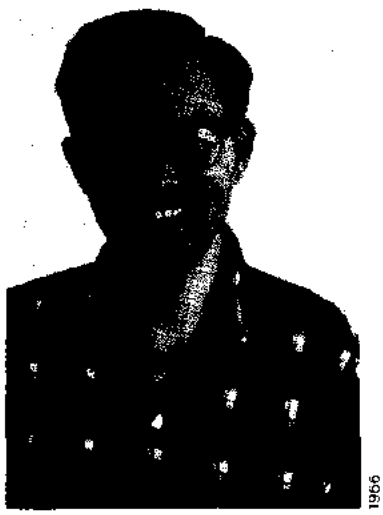

Plate 4.4. **A**: Thomas M. Mack (b. 1936), **B**: David B. Thomas (b. 1937) and **C**: Gordon G. Heiner (b. 1924), with Pakistani colleagues, conducted some of the most important and certainly the most comprehensive studies of the epidemiology of smallpox to be undertaken during the Intensified Programme. Working in what was then East and West Pakistan between 1965 and 1968, they demonstrated how surveillance and containment measures could be highly effective even in some of the most heavily infected areas.

SUMMARY

The basic facts of the epidemiology of smallpox may be summarized as follows:

(1) Smallpox was a specifically human disease; there was and is no known animal reservoir of variola virus (see Chapter 30).

(2) Compared with the infectious agents of many other human viral diseases, variola virions are relatively resistant to inactivation by physical and chemical agents; nevertheless, infection almost always involved the face-to-face contact of a susceptible subject with a person suffering from clinical smallpox.

(3) The detection and recognition of cases were relatively simple, since the rash was usually quite distinctive and occurred mainly on uncovered parts of the body.

(4) Subclinical infections with variola virus seldom occurred, except in vaccinated close contacts of cases. These individuals rarely, if ever, transmitted smallpox to others and were of little or no importance epidemiologically; almost all new cases could be traced to contacts with overt cases.

(5) An attack of smallpox was followed by death or recovery; persistent, latent or recurrent infection did not occur and cases were never infectious after the rash had gone.

(6) Different strains of variola virus differed in their virulence. Strains from outbreaks with case-fatality rates of about 1% in unvaccinated persons are designated variola minor virus. Most strains, for most of history, were associated with much higher case-fatality rates (5%–15%, and more commonly about 25%); these strains are designated variola major virus.

(7) All strains of variola virus are indistinguishable antigenically. In the vast majority of cases, immunity to reinfection was absolute. Similar protection could be reproduced, for a period of several years, by immunization with a live virus vaccine prepared from a related orthopoxvirus, such as cowpox or vaccinia virus.

(8) There was a pronounced seasonal incidence: smallpox was essentially a winter–spring disease.

(9) Smallpox spread rather slowly. There was an interval of 2–3 weeks between each generation of cases, and even during the transmission season an index case rarely infected as many as 5 other persons.

CHAPTER 5

THE HISTORY OF SMALLPOX AND ITS SPREAD AROUND THE WORLD

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INTRODUCTION

Smallpox was a disease with such obvious and characteristic clinical signs and caused such dramatic and disastrous epidemics that it was long the subject of myths and superstitions, and physicians and historians wrote much about it. This chapter provides a brief historical background, from the earliest civilizations until the beginning of the

20th century, of the occurrence of smallpox and its spread around the world. In compiling it we have drawn heavily on a recent book by Dr D.R. Hopkins: *Princes and Peasants. Smallpox in History* (Hopkins, 1983a), to which we refer readers interested in learning more about the way in which smallpox has influenced history, as well as about the history of smallpox and its control.

Smallpox was a specifically human infectious disease. One attack conferred lifelong immunity on survivors and neither chronic nor recurrent infectivity occurred among those who recovered from the acute illness. The persistence of such a disease in an endemic state within a human community was possible only if the population admitted a large regular accession of susceptible persons, either by birth or by immigration. Where appropriate and possible, estimates have been provided of the populations of some countries and continents at various times in the past, using the *Atlas of World Population History* (McEvedy & Jones, 1978) as a source-book. It must be emphasized that most of these population estimates are informed guesses rather than estimates based on reliable demographic data.

In order to provide an overview of the history of the world-wide spread and the subsequent control of smallpox, a list of important historical events that relate to this chapter and to Chapter 6 is provided in Table 5.1.

SMALLPOX BEFORE AD 1000

Most of the early civilizations left written records, some of which describe diseases of the time. Medical historians have been able tentatively to identify some of these diseases, but the older the records the less reliable are the diagnoses. Unmistakable descriptions of smallpox did not appear until the 4th century AD in China, the 7th century in India and the Mediterranean, and the 10th century in south-western Asia. Each of these descriptions refers to what was at the time a well-known disease. Mummified human remains provide another kind of evidence of disease, which is potentially more reliable than the interpretation of ancient writings, but suitable material is very scarce. It is therefore necessary to use epidemiological intuition to make guesses about the earliest occurrence of smallpox as a human disease.

Egypt

One of the earliest concentrations of civilized man was in the valley of the Nile and in the Fertile Crescent, which stretched from Palestine to the flood plains of the Tigris and the Euphrates. Trade and conquest made this region a single ecological unit, as far as the transmission of many human diseases was concerned. However, apart from reference to a "plague" that the Hittites were said to have caught from the Egyptians in the 14th century BC, which could conceivably have been smallpox, the written records of these civilizations, which include the Talmud and the Bible, do not refer to any disease that can be interpreted as being smallpox.

The largest and densest population in the region was in the valley of the Nile, where there may have been 1 million persons in the 3rd millennium BC and perhaps 3 million by the 1st millennium BC. As biblical and other written sources attest, Egypt was periodically visited by devastating epidemics, but none has been described which was suggestive of smallpox. However, the Egyptian practice of mummification preserved the skin, musculature and bones of a large number of royal personages, and diagnoses of the causes of death of several mummified persons have been made by palaeopathologists (Ruffer, 1921). The scientific literature mentions 3 mummies whose skin was covered with lesions that looked like those of a smallpox rash.

Ruffer & Ferguson (1911) described a smallpox-like eruption on the mummy of a middle-aged man who had died during the Twentieth Dynasty (1200–1100 BC). Section of a portion of skin showed dome-shaped vesicles in the epidermis, similar to those found in smallpox. Considering how resistant poxvirions are and how well preserved material from Egyptian mummies can sometimes be (Lewin, 1967), it is unfortunate that electron microscopy was not available at the time of this discovery, and that tissue from "smallpox" mummies has not thenceforth been at the disposal of investigators for electron microscopic examination. Ruffer (1921) mentioned that there was a similar eruption on a mummy of the Eighteenth Dynasty (1580–1350 BC) and on the mummy of Ramses V, who died as a young man in 1157 BC (Plate 5.1). Hopkins (1983a) describes some features of the burial of Ramses V that are consistent with a diagnosis of smallpox, and in 1979 he was able to examine the mummy himself:

Plate 5.1. The mummified head of Ramses V of Egypt (died 1157 BC) showing the pustular eruption that may have been due to smallpox. (From Smith, 1912.)

"It is one of the best preserved royal mummies in the [Cairo] museum. Inspection of the mummy revealed a rash of elevated 'pustules', each about two to four millimeters in diameter, that was most distinct on the lower face, neck, and shoulders, but was also visible on the arms. Over the shoulders especially, these pustules were pale yellow against a dark brown-reddish background, the latter partly due to cosmetic compounds used in royal mummifications during that period. On his upper face, only smaller raised pimples (one to two millimeters) could be seen, which might have been shrunken more by tighter wrappings over the forehead. It was not possible to examine the palms or soles where the presence of pustules would be highly characteristic of smallpox, because his arms were folded across his chest with the palms down, and the shroud was stuck to his soles. No such rash could be seen on the chest or upper abdomen. Earlier photographs of this mummy, published by G. Elliot Smith (1912) show that the rash is also prominent on the lower abdomen and scrotum ... Three folds in the skin over the left cheek suggest that his face may have been swollen when he died. The appearance of the larger pustules and the apparent distribution of the rash are similar to smallpox rashes I have seen in more recent victims."

One might have expected that an epidemic disease as distinctive as smallpox, which killed pharaohs and nobles as well as the common people, would have been described in the extensive writings on medical subjects left by the Egyptians, or by their northern neighbours in Asia Minor. However, no such description exists, although in the Ebers Papyrus there is a passing reference to an illness affecting the skin which Regöly-Mérei (1966) suggests may have been smallpox.

There remains the tantalizing speculation, based on these 3 mummies, that smallpox may have occurred among the inhabitants of Egypt more than 3000 years ago, which is well over a thousand years earlier than any reliable references to the disease elsewhere in the ancient world. From here it could well have been carried to India during the 1st millennium BC, either overland by caravan or, more likely, by sea.

India

Although there may have been a population of some 5 million in the Indus valley during the 2nd millennium BC, this civilization collapsed and disappeared about 1600 BC. A thousand years later another civilization, based on rice-growing, developed further east, and by 500 BC the Indian subcontinent had a population of about 25 million, of whom some 15 million lived in the Ganges basin, which has remained the demographic centre of the subcontinent ever since.

Holwell (1767), a physician of the British East India Company who survived imprisonment in the Black Hole of Calcutta, suggested that smallpox had existed in India from "time immemorial", and stated that it was mentioned in the most ancient Sanskrit writings, the *Atharva Veda*. Holwell's suggestions have been quoted by Hirsch (1883) and Hopkins (1983a), among others, as evidence of the occurrence of smallpox in India from very early times. Nicholas (1981), a scholar of Indian history and anthropology, contests this view.

He noted that *masūrikā*, the word used for smallpox, is found in many medical compilations produced in India since the beginning of the Christian era, but not in the more ancient *Atharva Veda*. It first appears in the compilations of Caraka and Suśruta, which were begun before the Christian era and put into their final forms in the 4th century AD. But according to Nicholas these texts say very little about *masūrikā* and refer

Table 5.1. Important events in the history of smallpox, from ancient times to 1900

Period	Africa	Americas
2nd millennium BC	? smallpox in 3 Egyptian mummies.	
1st millennium BC		
1st century AD		
2nd century		
4th century		
5th century		
6th century		
7th century	Ahrun of Alexandria describes smallpox (622).	
8th century		
10th century	Smallpox probably spread to western Africa by Arabs.	
13th century	Variolation by cutaneous route introduced into Egypt by Mamelukes.	
14th century		
15th century		
16th century	Smallpox epidemic in eastern Africa (1589). Smallpox introduced into coastal ports of western Africa.	Smallpox introduced into Caribbean (Hispaniola) (1507). Smallpox spreads from Hispaniola to Mexico (1520). Smallpox spreads to Peru (1524). Smallpox in Brazil (1555).
17th century		Severe smallpox outbreak in Massachusetts, USA (1617). Severe outbreak in Brazil (1665–1666).
18th century	Smallpox introduced into Cape Town and destroys Hottentots (1713 and 1755). Smallpox spreads in central Africa with slave traders.	Variolation introduced into North America (1721). Smallpox disrupts Colonial army at Quebec (1776). Washington orders variolation of Continental army (1777).
19th century	Further spread of smallpox in eastern and central Africa with caravans (1840s). Variola minor ("amaas") described in South Africa (1890s; 1904).	Pandemics among North American Indians (1801–1802 and 1836–1840). President Jefferson initiates vaccination of American Indians (1801). President Lincoln has smallpox (1863). Variola minor occurs in Florida and spreads throughout USA (1896–1900s).

Table 5.1. *(continued)*

Asia and Oceania	Europe
Epidemic spreads from Egypt to Hittites (~1350 BC) ?? smallpox.	
Compilation of *Suśruta Samhita* in India (~100 BC). Mentions *masūrikâ*, which may be smallpox.	Plague of Athens, from Egypt and Libya, spreads to Persia (430 BC). Epidemic in Sicily, from Libya (395 BC) ?? smallpox.
Smallpox introduced into China from south-west (48–49).	
	Antonine Plague spread to Rome from Mesopotamia (165) ?? smallpox.
Ko Hung in China differentiates smallpox from measles (340).	
	Bishop Nicaise of Rheims recovers from smallpox (450); becomes patron saint of smallpox.
"Elephant War" in Mecca (568) ? smallpox decimates Ethiopian soldiers. Smallpox spreads from China to Korea (583) and from Korea to Japan (585).	Gregory of Tours describes ? smallpox in France and Italy (580). Bishop Marius uses term "variola".
Arabs carry smallpox with invading armies to North Africa and Spain.	
Al-Razi publishes descriptions of smallpox and measles (910). First use of modern Chinese character for smallpox. First use of variolation by intranasal route in China as secret rite. *Ishinho* published in Japan (982); describes "red treatment" and isolation hospitals.	Daughter of King Alfred of England has ? smallpox.
	Gilbertus Anglicus describes clinical types of smallpox in England (1240); recommends "red treatment". First introduction of smallpox to Iceland from Denmark (1241).
King of Burma dies of smallpox. Epidemic of smallpox in Siam.	
	Severe smallpox epidemic in Paris (1438).
King of Siam dies of smallpox (1534).	Records of deaths from smallpox maintained in Geneva (1580).
Severe epidemics in Siberia (1630). Variolation by nasal route popularized in China.	Severe smallpox in most of Europe. London Bills of Mortality record 10% of deaths due to smallpox (1629). First account of smallpox in Russia (1623). Sydenham describes clinical types of smallpox, and distinguishes measles from smallpox.
Chinese emperor sends variolation teams to control smallpox in Tartary (Siberia) (1724). Variolation introduced into Japan (1744). Smallpox epidemics among aborigines in Australia (1789 and 1829).	Variolation introduced into Great Britain and Bohemia (1721). London Small-Pox and Inoculation Hospital founded (1746). Heberden distinguishes smallpox from chickenpox (1760). Dimsdale variolates Catherine the Great of Russia (1768). Smallpox cripples Spanish–French fleet attacking England (1779). Jenner describes vaccination (1798).
Vaccination introduced into India (1802), Philippines (1803), Java (1805), China (1805). Vaccination introduced into Siam (1840). Vaccination introduced into Japan (1849).	Vaccination spreads throughout Europe (1800–1801). Compulsory vaccination in Bavaria (1807). Revaccination proposed in Württemberg (1829). National Vaccine Establishment founded in England (1808). Negri in Naples begins systematic production of vaccine in cow (1845). Production in cows introduced in France (1864). Last great epidemic in Europe, after Franco-Prussian War (1870–1871). Copeman demonstrates bactericidal effect of glycerol (1892).

to it as a trivial skin disease. The first extant description of *masūrikā* as a severe and sometimes fatal disease appears in the works of Vagbhata, a physician writing early in the 7th century AD. A century later the *Nidana* of Madhava-kara included an extensive and knowledgeable chapter on *masūrikā*, treating smallpox, chickenpox and measles together. Wise (1867) suggested that the failure of earlier Indian writings to identify *masūrikā* as a severe disease indicates that smallpox may have changed its characteristics not long before al-Razi, towards the end of the 1st millennium AD, in Baghdad, described the disease as we now know it (see below). However, Chinese descriptions identify smallpox as a serious disease that was imported from the west, apparently as early as the 1st century AD.

The only suggestion of the possibly earlier existence of smallpox in the Indian subcontinent was the epidemic that attacked Alexander's army in 327 BC, when it was camped on the lower Indus, but although "scabs" are mentioned the description is so incomplete that it is difficult to be at all certain of the diagnosis.

We can speculate that smallpox was brought to India by Egyptian traders during the 1st millennium BC, to become endemic in the large population of the Ganges valley. However, there is no reliable evidence of its existence there before the description in the *Suśruta Samhita*, which appears to relate to a rather trivial skin disease rather than a generalized infection with a high mortality.

However, for the last 1500 years smallpox has been known to be endemic in India, especially in the densely populated agricultural settlements of the Ganges plain. Periodic epidemic episodes occurred then, as they continued to do until the disease was eradicated in the latter part of the 20th century.

South-western Asia

Apart from the problematic epidemic among the Hittites, already referred to, the earliest reference to an epidemic disease that may have been smallpox is the description of a plague that afflicted the Ethiopian invaders of Mecca in Arabia in AD 568, in what was called the "Elephant War" (Moore, 1815). The Ethiopian soldiers were afflicted by a severe illness characterized by a rash, which almost totally destroyed the invading army and ended Ethiopian rule in Arabia.

Scholars in south-western Asia and in Alexandria, on the Egyptian Mediterranean coast, produced notable works on smallpox long before European physicians did. Ahrun, a Christian priest who lived in Alexandria 30 years before the Arab conquest of Egypt, wrote clear descriptions of smallpox and measles in AD 622 (Moore, 1815):

> "When the smallpox pustules are white and red, they are healthy; when green and black, malignant; and if, after a time, the eruption of smallpox and measles changes to a saffron colour, and the fever moderates, good hopes may be entertained; but if these eruptions appear during a frenzy fever, they are fatal."

The most notable of these writings, however, is that of al-Razi (Abu-Bakr Muhammad Ibn Zakariya, al-Razi (Rhazes)), the great Persian-born physician who was in charge of the hospital at Baghdad. Al-Razi's treatise on smallpox and measles was translated into Latin and Greek and influenced European physicians until the 17th century and even later (al-Razi, 910).

Besides clearly distinguishing between smallpox and measles, as Ko Hung in China had done 6 centuries earlier (see below), al-Razi made some astute epidemiological observations on smallpox, describing its seasonal incidence (most common in spring) and the fact that it was primarily a disease of children.

Another great Persian scholar, Avicenna (980 1037), also wrote on smallpox; translations of his works into Latin influenced medical practice in Europe in Renaissance times.

Europe

During the classical era Greece was the only densely populated part of Europe, with a population of about 3 million in 400 BC. By the beginning of the Christian era emigration had reduced the population to about 2 million and the centre of gravity of the population of Europe had shifted to Rome.

There are no unequivocal records of smallpox in Europe before the 6th century AD, but it has been suggested that it was a major component of the "Plague of Athens" that occurred in 430 BC, during the Peloponnesian Wars, and was described by Thucydides. This affliction was said to have originated in "Ethiopia" and spread to Egypt and Libya before crossing the Mediterranean to the port of Piraeus and thence reaching Athens.

From Epidemics to Endemicity

The earliest writers on smallpox whose descriptions are now universally accepted—Ko Hung in China, Vagbhata in India and al-Razi in Asia Minor—describe smallpox as primarily a disease of children. This is a mark of well-established endemicity and was the result primarily of demographic factors. Alivizatos (1950) noted that smallpox was repeatedly imported into Germany by the Crusaders towards the end of the 12th century. It began to cause extensive epidemics only by the 14th century, eventually becoming a disease in which the majority of cases occurred in children (it was given the name *Kinderblättern*) only at the end of the 17th century. The change occurred more rapidly than this in more densely populated countries (for example in Mexico, see below), but in most places it probably took several human generations. Thus the classical early descriptions of smallpox as a disease primarily affecting children argue for the presence of smallpox in the area concerned (for example in south-western Asia, following al-Razi's description) some centuries earlier.

Except for the absence of any reference to residual pockmarks in those who recovered, Thucydides' description has suggested to several medical historians (Zinsser, 1935; Alivizatos, 1950; Littman & Littman, 1969) that the epidemic may have been due to smallpox. It lasted for over 2 years and devastated the Athenian army.

According to some authorities (Alivizatos, 1950), an epidemic that prevented the Carthaginians from gaining control of Sicily, at the siege of Syracuse in 395 BC, may also have been smallpox. The next speculative suggestion of smallpox in Europe was its possible role in the Antonine Plague, which appeared to start in a Roman army fighting in Mesopotamia in AD 164. Returning soldiers brought an infectious disease to Syria and Italy, where it raged for 15 years and greatly weakened the Roman empire. The clinical features were described, rather inadequately, by Galen, and, more recently, in a critical analysis of the evidence Littman & Littman (1973) argue convincingly that the principal disease that occurred in the Antonine Plague was probably smallpox.

Apart from Rome, there were few centres of population in Europe large enough at that time to have supported endemic smallpox, but various epidemics from the 5th century onwards have been ascribed to the disease. St Nicaise, the Bishop of Rheims, who is said to have suffered from smallpox, was beheaded by the Huns in AD 452 and was later accepted as the patron saint of European victims of smallpox. During the 6th century smallpox may have occurred as an endemic disease with epidemic episodes, one of which was described by Bishop Gregory of Tours, but Moore (1815) considers that this outbreak was due to bubonic plague. At about this time Bishop Marius of Avenches (near present-day Lausanne, in Switzerland) used the Latin word "variola" for the first time (from *varius* = mottled, or *varus* = a pimple) to describe the epidemic illness then present in Italy and France. It was not until 5 centuries later that Constantinus Africanus first explicitly limited the use of the word "variola" to the disease we call smallpox.

There is a dearth of information on smallpox, as on most subjects, for the remainder of the Middle Ages. However, it undoubtedly accompanied the armies of Islam across North Africa in the 7th century and spread into Spain and Portugal with their conquest in 710. The Germanic warriors crushed the Moors when invasion of France was attempted in 731, but smallpox and measles remained in France as legacies of the Moors. Smallpox may also have occurred from time to time in other parts of Europe following importations from endemic areas, and by the latter half of the 10th century it was a relatively common disease in most of the Arab-controlled areas of North Africa and Europe.

China and Japan

The earliest agricultural society of China comprised about 1 million peasants dependent on wheat-growing, in the valley of the Huang Ho river in 3000 BC. The population

grew steadily, until by 400 BC there were some 25 million people living in the northern half of China proper, mostly in the valleys of the Huang Ho and Yangtse rivers. After the political unification of China in 221 BC the population grew to about 50 million and fluctuated around that number until AD 1000, when there was a demographic explosion fostered in part by fuller exploitation of the rice-growing potential of the Yangtse valley.

In contrast to the speculations on the existence of smallpox from very early times in Egypt and India, there is general agreement that smallpox was introduced into China from outside the country. According to Needham & Lu (in press), the earliest description of smallpox and its origins in China occurs in the *Handbook of Medicines for Emergencies*, which was completed by the great physician Ko Hung in AD 340:

"Recently some people have suffered from seasonal epidemic sores which attack the head, face and trunk. In a short time they spread all over the body. They look like red boils, all containing some white matter. The pustules arise all together, and later dry up about the same time. If the severe cases are not treated immediately many will die. Patients who recover are left with dark purplish scars the colour of which takes more than a year to fade ... People say that it first appeared from the West in the fourth year of the Yung-Hui reign-period, and passed eastwards, then spreading all over the country ... Another saying is that in the Chien-Wu reign-period prisoners of war brought it back from Nan-yang, and for this reason one of its names is still 'prisoners' pox'."

Needham & Lu (in press) point out that there are difficulties in giving accurate dates for the periods mentioned in this text, but they conclude that the likely date for the introduction of smallpox was in the years between AD 25 and AD 49, when Ma Yuan was subduing the aboriginal tribal people of Hunan province. Following Hirsch (1883) and Macgowan (1884), Hopkins (1983a) suggests that there may have been an earlier introduction than this, from "Huns" in the north in about 250 BC. If so, as Macgowan suggests, it died out and had been forgotten. From about the 2nd century AD smallpox was established as an endemic disease in the densely populated river valleys; there are references from the latter part of the 6th century onwards to pockmarked persons and to various treatments for smallpox.

Japan consisted of a group of sparsely inhabited islands with a total population of less than 5 million in AD 1000; most of the islands were too small and too thinly populated to support endemic smallpox. There were nevertheless repeated introductions from China and Korea. As early as the 6th century cultural and trading contacts were increasing between China and Japan, both directly and via Korea. Buddhism was first introduced into Japan from Korea in AD 552, and further contacts were made later that century. Smallpox was introduced at about the same time, and the Japanese were perplexed to know whether to ascribe the pestilence to their indigenous Shinto gods or to the new Buddha. There were repeated reintroductions during the 7th and 8th centuries. Nara, the first real city in Japan, was established in 710; in 735 smallpox, introduced by a shipwrecked sailor, devastated the city of half a million inhabitants and killed many of the nobles. Smallpox continued to be the focus of religious argument between the Shinto priests and the adherents of Buddhism, and in 748 the great bronze statue of Buddha, the *Nara Daibutsu*, was completed, having been commissioned by the Emperor to put an end to his troubles with smallpox. Endemic smallpox was established in Japan during the 10th century, but there were still recurrent severe epidemics that affected villages and towns in which the endemic disease did not occur.

Summary: the Spread of Smallpox from Antiquity until AD 1000

It is impossible to do more than guess about the original home of smallpox, which may have developed as a specifically human disease at any time after irrigated agriculture had allowed human populations to grow sufficiently large, perhaps some 6000 years ago. The major contenders for the doubtful honour are Egypt and India. It is reasonable to argue that smallpox was endemic in the densely populated Nile and Ganges river valleys at the beginning of the Christian era. From there it spread west to south-western Asia and made periodic incursions into Europe, but was not properly established around the Mediterranean littoral until the armies of Islam drove through North Africa into the Iberian Peninsula in the 8th century. As population size increased in various parts of Europe, endemic smallpox extended, so that it was probably known throughout south-western Asia and the Mediterranean

littoral of Africa and Europe by the end of the 10th century. Al-Razi published his detailed and percipient account of smallpox and measles about AD 910.

Early in the Christian era smallpox was carried to the east, first with warring armies and later with traders who moved along the Burma Road in the south and the Silk Road in the north. Smallpox was probably already established as an endemic disease in China by the 4th century, when Ko Hung differentiated between smallpox and measles, some 600 years before al-Razi. Subsequently, as contacts were developed between China and Korea and Japan, smallpox was repeatedly imported into the two latter countries, to become endemic there during about the 10th century.

By the end of the 10th century, therefore, smallpox was probably endemic in the more densely populated parts of the Eurasian land mass and along the Mediterranean littoral of Africa. There were still many uninfected localities, but the stage was set for endemicity with periodic explosive epidemics, a situation that characterized the 16th and 17th centuries in Europe, when this disease then spread to most of the inhabited world. Fig. 5.1 presents a possible scenario of the spread of smallpox throughout the Eurasian land mass and to adjacent countries up to the end of the 1st millennium AD.

SMALLPOX IN SOUTHERN ASIA BETWEEN 1000 AND 1900

The Indian Subcontinent

With a population of 25 million by 500 BC, already dense enough in the valley of the Ganges to support endemic smallpox, the population of the Indian subcontinent rose steadily over succeeding centuries to reach about 80 million by AD 1000 and 100 million by 1500. Thereafter it rose somewhat more rapidly, to 185 million by 1800, and then exploded, exceeding 280 million in 1900.

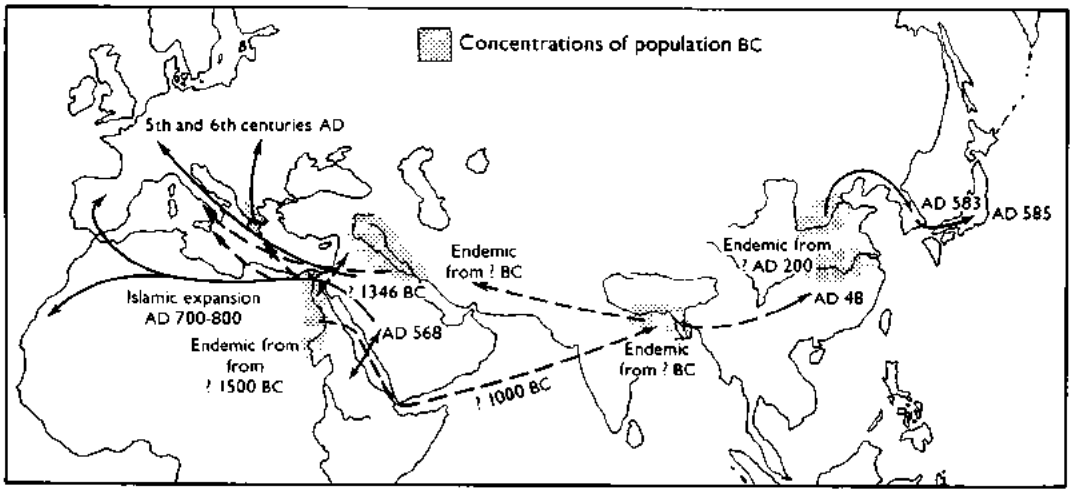
Smallpox was probably present in India for over 2000 years and remained endemic there until its final eradication from the subcontinent in 1975. Apart from the writings of Vagbhata and allusions to the Hindu goddess of smallpox, Śītalā (see Plate 5.2), there is little historical evidence of smallpox in India until after 1500, when European commentators began to report on various aspects of Indian life. The ecological and demographic conditions in India were such that the pattern of endemicity with seasonal (spring) epidemics that was observed after 1500 had probably prevailed for a millennium before that.

The earliest European accounts of smallpox came from the Portuguese enclave of Goa, where 8000 children are said to have

Inoculation, Variolation and Vaccination

When the practice of deliberately introducing material from smallpox patients into the skin of susceptible subjects was introduced into Great Britain early in the 18th century it was called "inoculating the smallpox" or "inoculation". With Jenner's replacement of material from smallpox patients with fluid from cowpox lesions in 1798, from cows or humans, it became necessary to distinguish inoculating the cowpox from inoculating the smallpox. At first the term "vaccine inoculation" was used; later, Jenner's practice came to be called "vaccination" and the inoculation of material from smallpox patients was called "variolation". In this book we have used the terms inoculation and variolation as synonyms, reserving "vaccination" for procedures involving cowpox or vaccinia virus.

Variolation was always carried out with material from the pustules or scabs of patients. After animal vaccines were introduced during the latter part of the 19th century, vaccination was usually carried out with vaccine "lymph" from cows. However, before that time the virus was maintained by arm-to-arm vaccination of children, and was sometimes shipped over long distances as "vaccine scabs", as well as being dried on threads or ivory points (see Chapter 6).



"Plagues": ? smallpox	Writers or books	Place	Date
Hittites 1346 BC	Suśruta	India	? BC
Syracuse 595 BC	Ko Hung	China	AD 340
Athens 430 BC	Ahrun	Alexandria	AD 622
Antonine AD 165	Vagbhata	India	AD 600–700
Mecca AD 568	Al-Razi	Baghdad	~ AD 910
	Ishinho	Japan	AD 982

Fig. 5.1. Possible early sites of outbreaks and routes of spread of smallpox in the ancient world. "Plagues" are historical episodes of epidemic disease reported in ancient and classical literature, which may have been due to smallpox. "Writers" refer to physicians who wrote the principal descriptions of smallpox before the end of the 1st millennium AD.

died in an outbreak in 1545. Scattered references occur to outbreaks of smallpox accompanying military campaigns in Ceylon and on the Indian mainland, but more complete descriptions date from the 18th century, after the beginning of *de facto* British rule in India in 1757.

A decade later, Holwell (1767) described a situation in Bengal which remained characteristic of smallpox in many parts of India during the succeeding 2 centuries: endemic disease with spring (dry season) maxima, punctuated by outbreaks of epidemic intensity every 5–7 years. There were droughts, floods, famine and a particularly severe epidemic of smallpox in Bengal in 1769–1770.

Although variolation had been known for centuries in India, it was nowhere practised on a large enough scale to be of importance as a public health measure. It protected individuals, but its spread from inoculated persons contributed to outbreaks of smallpox. In 1802 the Swiss physician Jean de Carro, who then lived in Vienna and was an enthusiastic supporter of Jennerian vaccination, succeeded in sending viable vaccine to Bombay, via Baghdad. Although at first viewed with suspicion as a British trick, vaccination spread, initially more rapidly in Ceylon than in India. However, during the first half of the 19th century smallpox continued to take its toll. For example, superimposed on the endemic background were 4 major epidemics in Calcutta during the first half of the 19th century: in 1832–1833, 1837–1838, 1843–1844 and 1849–1850.

During the second half of the 19th century, statistical reports of the occurrence of various infectious diseases were compiled which always ranked smallpox as one of the leading causes of death in India. For example, during the 10 epidemic years of 1868–1869, 1872–1874, 1877–1879 and 1883–1884 (Fig. 5.2), at least 2.5 million out of the estimated 180 million people in British India were reported to have died of smallpox, and experience in the 20th century suggests that there was gross underreporting of deaths as well as of cases. Even in a non-epidemic year, as many as 100 000 deaths from smallpox were reported. Many of the epidemics in India, up to the time of eradication, were intensified by crowding and poverty and the vast movements of people associated with religious festivals,

Gods, Goddesses and Saints Associated with Smallpox

A feature of human reactions to smallpox that demonstrates its impact was the association of specific gods, goddesses and saints with the disease (Plates 5.2–5.5). Hopkins (1983a) describes these deities and saints in some detail; the characteristics of the best known are briefly noted here.

In Europe, *St Nicaise*, the Bishop of Rheims, who was killed by the Huns in 452, shortly after he had recovered from an attack of smallpox, became the patron saint of smallpox and was revered during the Middle Ages. Subsequently, the Reformation and the greater menace of plague (which threatened all adults as well as children, whereas endemic smallpox was by then mainly a disease of children) led to the neglect of St Nicaise.

Śītalā (*Shitala*) *mata* appears to have been an Indian folk goddess from early times, whose association with smallpox dates from a later period (Nicholas, 1981). However, from about the 18th century onwards Śītalā was closely associated with smallpox and was a widely patronized goddess, with temples and shrines all over India. It will be interesting to see what changes occur in the worship of Śītalā now that smallpox has been eradicated from India.

T'ou-Shen Niang-Niang was a goddess of smallpox in China. Tradition traces her worship to an 11th century Buddhist nun who is credited with introducing variolation into China (see Chapter 6), and during the mid-19th century she was one of the most popular objects of worship among the people at large, irrespective of their religious affiliations. Temples were erected to her all over China.

In Japan, a red picture of *Tametomo*, a 12th century hero who was reputed to have thwarted a smallpox demon, was often hung in the rooms of smallpox victims to aid their recovery. The colour red had an ancient and persistent association with smallpox, and was supposed to promote recovery (see Hopkins, 1983a).

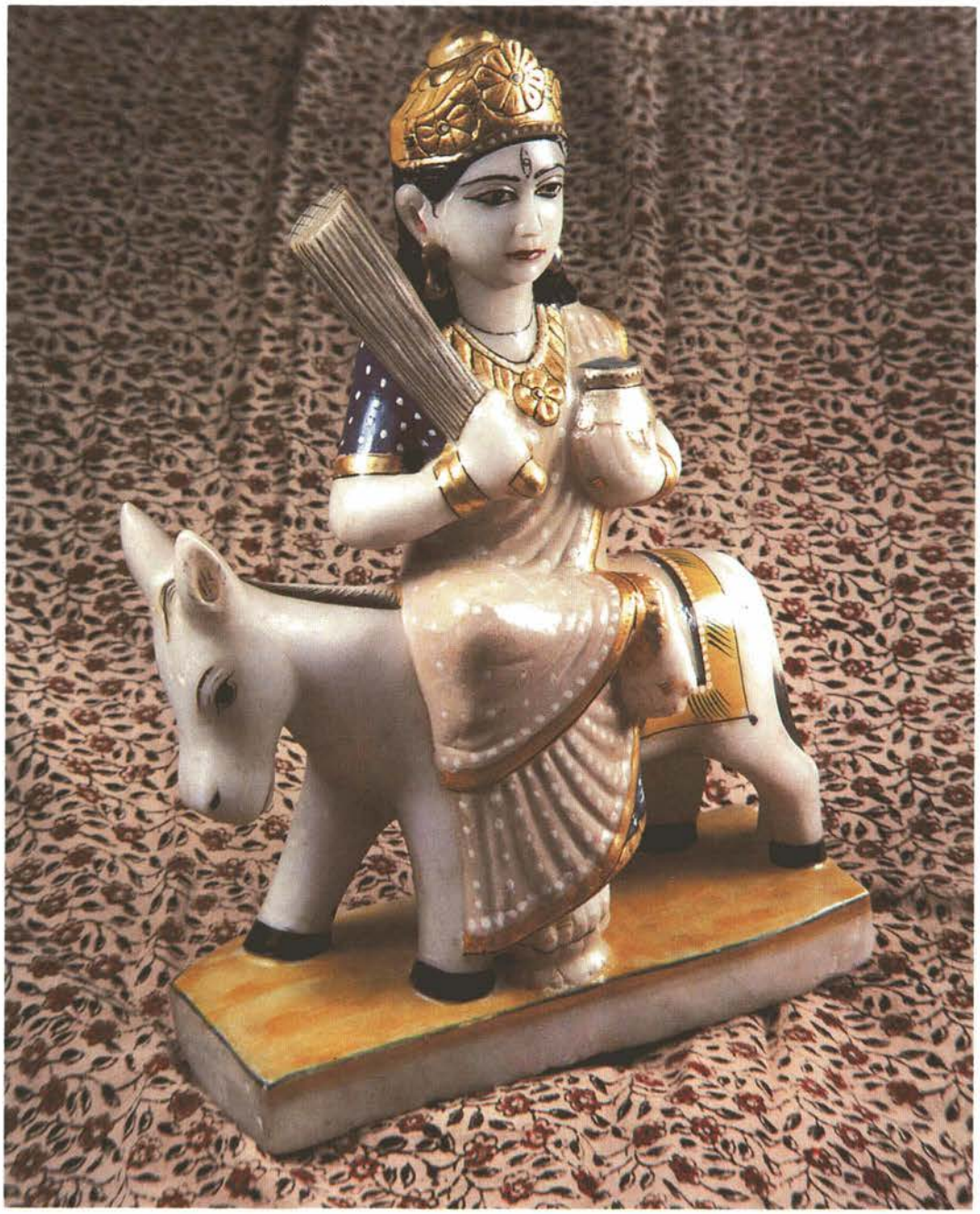
In Africa, worship of *Sopona*, a smallpox deity, existed among the Yorubas and some of their neighbours in south-west Nigeria, Benin and Togo, having been introduced from the north at the beginning of the 18th century. Formal worship of Sopona was controlled by *féticheurs*, who were in charge of the shrines and carried out variolation. Sometimes *féticheurs* were suspected of spreading smallpox. When they were transported to Brazil as slaves, some of the Yoruba-speaking people took Sopona with them, although he was more generally known by another of his names from western Africa, *Obaluaye* ("King of the Earth") or *Omolu*.

famines and wars. Although many adults were attacked, in the majority of cases and deaths the victims were infants and young children. In India at this time, as was the case a century earlier in Europe, there was a popular saying that children should not be regarded as permanent members of the family, for purposes of inheritance, until they had recovered from smallpox. Facial pockmarks were the rule among adults, and blindness, for which smallpox was often responsible, was common.

Against a background of endemic smallpox, a steady succession of major epidemics, peaking every 5–7 years, continued after the great epidemic of 1883–1884 but at a much lower level, because of the cumulative effect of steadily increasing vaccination (see Fig. 5.2). Nevertheless, in many parts of the subcontinent vaccination was not extensively practised until the 1950s. India and countries adjacent to it remained the major focus of smallpox in the world until 1975, when eradication was achieved there.

Burma, Siam and Indochina

The population histories of the countries between India and China—Burma, Siam (Thailand) and Indochina (comprising present-day Democratic Kampuchea, Lao People's Democratic Republic and Viet Nam)—are rather similar, although until 1900 the population of Siam was only about half that of the other two. Two thousand years ago the populations of Burma and Indochina each numbered about 1 million (0.5 million for Siam). They had doubled by AD 1000 and doubled again by 1500. By 1800 the popula-



Z. KAREEM

Plate 5.2. *Sītalā Mata,* the Hindu goddess of smallpox.

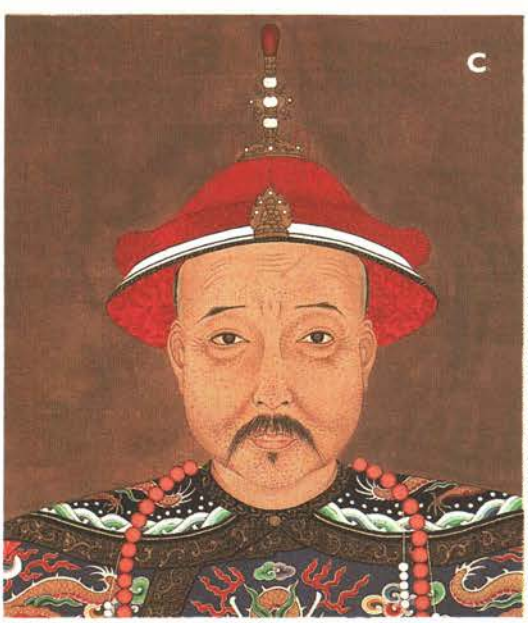
White-bodied one, mounted on an ass, in your two hands a broom and a full pot,
To mitigate fever, you asperse, from the full pot, with the broom,
the water of immortality.
Naked, with a winnowing fan on the head, your body
adorned with gold and many gems, three-eyed,
You are the quencher of the fierce heat of pustules;
Śītalā, I worship you.
(Quoted in Nicholas, 1981.)

A

JAPANESE ASSOCIATION FOR THE PRESERVATION OF MEDICAL CULTURE

B

N. BOUVIER



C

METROPOLITAN MUSEUM OF ART, NEW YORK

Plate 5.3. **A:** Chinzei Hachiro Tametomo (1139–1170), a skilful archer, was exiled to the island of Oshima. He is reputed to have prevented a smallpox demon from landing there. His image was hung on the walls of Japanese homes to help to protect them against smallpox. **B:** Drawing of patients with smallpox in Mexico in the year 1538. (Detail from *Codex telleriano-remensis,* in the Bibliothèque nationale, Paris.) **C:** K'ang Hsi, Emperor of China, 1661–1722. Although the third son, the pockmarked K'ang Hsi was chosen as emperor after his father died of smallpox in 1661. Unlike previous Manchus, he variolated his children and his troops. (Detail from a 19th century portrait.)

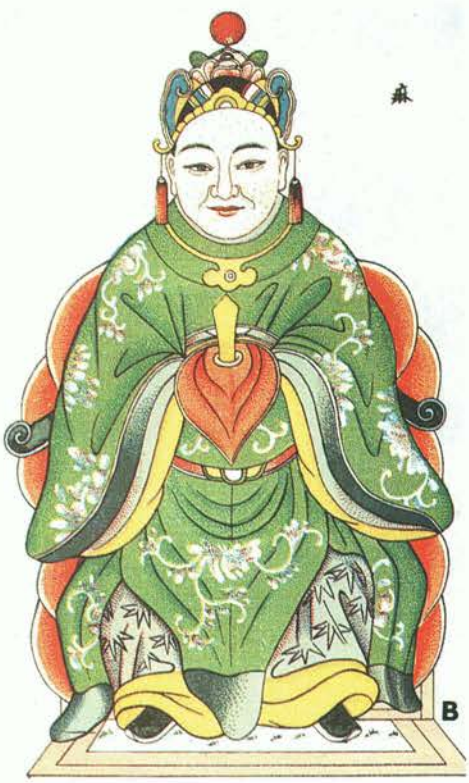


Plate 5.4. **A:** T'ou-Shen Niang-Niang, the Chinese goddess of smallpox. **B:** Ma-chen, the god who heals the scars of smallpox. **C:** Pan-chen, the god prayed to in black smallpox. (From Doré, 1915-1925.)

Plate 5.5 African gods of smallpox. **A:** Sopona, smallpox god among the Yorubas of western Africa. **B:** Yorubas who were taken to South America as slaves took their gods with them. Sopona was in time transformed into Omolu/Obaluaye.

The Significance of Epidemics

Devastating epidemics of smallpox created a deep impression on the population, and all histories of smallpox are punctuated with lists of the years of the major epidemics. It is important to distinguish two ecologically distinct situations in which such epidemics occurred. The first was when smallpox was introduced into a place in which it had not occurred previously, or at least not for many years, so that a large segment, perhaps all, of the population was susceptible. This led to epidemics that affected all age groups, and because of the great social disruption caused by the simultaneous illness of most of the bread-winners in a subsistence society, such epidemics were associated with very high death rates. In small populations, whether on islands such as Iceland or in the early colonial settlements in North America, the disease finally died out for lack of susceptible subjects. Further epidemics some years later would occur when fresh importations of smallpox encountered populations with adequate numbers of susceptible persons composed of hitherto unexposed children or immigrants.

The second situation in which "epidemic years" were recorded was in populous areas in which smallpox was always present as an endemic disease, as in Europe in the 18th century and the Indian subcontinent until 1975. For a variety of reasons—demographic, climatic and, in later years, the activity of vaccinators—the population of susceptible persons and optimum conditions for transmission fluctuated so that epidemic exacerbations occurred every few years, against a background of endemicity. In this latter situation disruption of the community was much less severe, because there were always many smallpox-immune bread-winners.

tions of the 3 countries were 6 million, 3 million, and 6.5 million respectively; population growth then took off, doubling during the next century.

There is only scanty information on smallpox in these countries prior to the late 19th century. A king of Burma died of smallpox during a military campaign in 1368, and variolation is said to have been introduced into Burma in 1785 from the recently annexed province of Arakan. From the mid-19th century Burma was administered as part of British India, and its smallpox statistics are included in the Indian records (Annual Reports of the Public Health Commissioners with the Government of India).

Siamese writings refer to epidemics of what was probably smallpox during the 14th century, and from the 16th century onwards there are repeated references to *thoraphit* and *ōk fī dāt* (the formal and familiar Siamese words for smallpox), with severe epidemics in 1563–1564, 1621–1623, 1749–1750 (Terweil, 1987). These Siamese writings were confirmed by the French writer de la Loubère in the late 17th century: "In a word, there are some contagious diseases but the real Plague of this Country is the Small Pox: it often makes dreadful ravages, and then they inter the bodies without burning them" (Loubère,

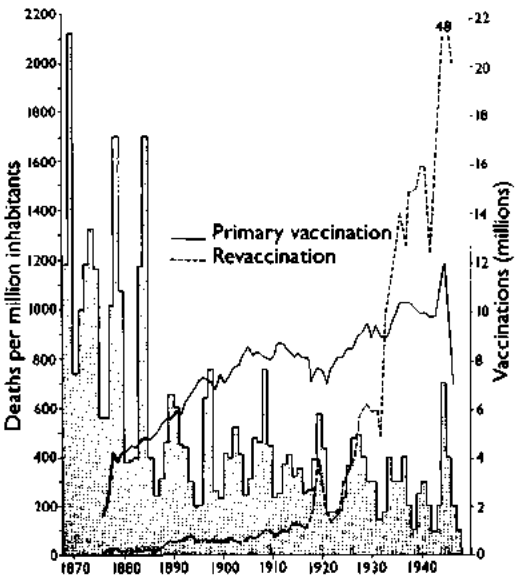


Fig. 5.2. Reported numbers of deaths from smallpox per million population in British India from 1868 to 1947, and the numbers of primary vaccinations and revaccinations from 1875 onwards. Epidemic peaks occurred about every 5 years throughout this period. (Data from Annual Reports of the Public Health Commissioners with the Government of India.)

reprinted 1969). Vaccination was introduced into Siam in 1840, shipments of vaccine scabs

being sent from Boston, USA, in 1840, 1844, 1846 and 1861, through Christian mission societies.

Severe epidemics continued to occur in Siam and Indochina during the latter part of the 19th century, the mortality among children in some epidemics being so great as to have a prolonged demographic effect because of the paucity of nubile women. As late as 1898, 95% of adolescent children in northern Viet Nam were pockmarked and nine-tenths of all blindness was ascribed to smallpox.

South-western Asia

Between the Indian subcontinent and Europe lies part of the Eurasian land mass that is variously described as south-western Asia, the Near East and the Middle East. It comprises present-day Afghanistan, Iraq and the Islamic Republic of Iran, the Arabian Peninsula, including its Mediterranean littoral, and Turkey-in-Asia. In 1800 none of these countries had a population of more than 9 million. However, Turkey, Arabia and Persia (Iran) had supported populations of some 4–5 million for the previous 2 millennia, and they were of major importance as centres of culture during the Dark Ages of Europe and as the corridor for trade, culture and conquest between Europe and the Indian subcontinent.

The work of Persian scholars, notably al-Razi and Avicenna, shows that smallpox was endemic in many parts of south-western Asia from at least the 6th century. Early in the 7th century, inspired and united by Mohammed's teachings, Arab armies began their war of conquest and took smallpox with them to Persia, across western Asia and northern Africa and into Spain, which was conquered in 710.

Although by the time they had reached adult life most persons would have been immune to the disease, smallpox affected several of the rulers of the Arabian empire, killing one caliph, leaving three with pockmarks and blinding two others. In the 10th and 11th centuries, as Arab traders extended their voyages to the east coast of Africa and across the Sahara to western Africa, their expeditions introduced smallpox into Africa south of the Sahara (see below).

Variolation by cutaneous inoculation was practised in various parts of south-western Asia from early times. It is said to have been introduced into Egypt by the Mamelukes in the 13th century, and it was in Constantinople that Lady Mary Wortley Montagu and the physicians Emanuele Timoni and Jacob Pylarini learned of the procedure in the early 18th century (see Chapter 6). However, it does not appear to have been practised on a scale or in a way that mitigated the severity of smallpox in the community, although it was important in preserving the beauty of recruits to the imperial harems.

SMALLPOX IN EASTERN ASIA BETWEEN 1000 AND 1900

China and Korea

The population of China, which had remained at 50–60 million for the whole of the 1st millennium of the Christian era, doubled during the next 2 centuries as the rice-growing potential of the Yangtse valley was further exploited. Then in 1211 the Mongols began their conquest of China, a bloody war which killed some 35 million people. It was 1500 before the population reached the level (110 million) that it had attained 300 years earlier. Thereafter population growth surged ahead, apart from a set-back in the middle of the 17th century associated with the Manchu conquest, and by 1900 the total number of inhabitants had reached about 475 million.

Smallpox spread through the dense agricultural settlements of the Huang Ho valley and from about the 2nd century AD was established as a major endemic and epidemic disease in China and Korea. As early as the 4th century Ko Hung had written a good clinical description of smallpox (see above), and in the 11th century medical descriptions of smallpox were published by Ch'ien Chung-Yang (1040–1121), who popularized the modern Chinese character for smallpox (a combination of the characters for "lentil-bean" and "sickness"). At about this time worship of a goddess of smallpox, T'ou-Shen Niang-Niang (Plate 5.4A), began. Buddhist, Taoist and Confucian adherents paid tribute to the "Dame who controls smallpox", who was feared more than she was loved.

Although preventive inoculation (variolation) was probably introduced into China at about this time it appears to have been practised as a secret rite and on a small scale (see Chapter 6). It became a public practice during the first half of the 16th century (Needham, 1980), but was never widely used.

At the beginning of the 13th century China had a population of about 100 million, and

smallpox was established in the densely populated areas as an endemic disease, affecting mainly children. It was seen as a threat by the tribal peoples to the north. The Mongols, for example, who began their invasion of China at this time, regarded contacts with the Chinese as a grave danger, whether at horse fairs or in border raids. Four centuries later the leaders of the Manchus dreaded smallpox. In planning raids through weaks spots in the Great Wall in 1633, the Manchu Khan insisted that only officers who had had smallpox should be sent on these expeditions, since they would have to go through populations in which smallpox was endemic. When the Manchu dynasty was later established, care was taken to exempt both Manchus and Mongols from otherwise mandatory appearances in Peking (see box). Perhaps, as Manchus, they did not trust variolation; at all events, in 1661, the Shun-Chih Emperor, Aihsin-Chuch-lo Fu-lin, died of smallpox. The third son, the pockmarked K'ang-Hsi (Plate 5.3C), was chosen to be his successor precisely because he had already had smallpox; he reigned as Emperor of China from 1661 to 1722 (Spence, 1974). Unlike earlier Manchus, K'ang-Hsi had his regular troops inoculated against smallpox "as I did my own children".

Late in the 18th century the Tibetan leaders, the Dalai and Panchen Lamas, for a long time declined invitations to come to the court in Peking because of their fear of smallpox. In 1780 the Panchen Lama acceded to the invitation of Emperor Ch'ien-Lung, only to die of smallpox within a few weeks of his arrival. From this time onwards, variolation and, later, vaccination played increasing roles in the epidemiology of smallpox in China, but towards the end of the 19th century European visitors noted that it was difficult to find an adult Chinese entirely free from pockmarks and that persons blinded by smallpox were still very common.

Vaccination was first introduced into Canton and Macao in 1805 by the famous Balmis-Salvany Expedition organized by King Carlos IV of Spain (see Chapter 6). However, the practice was not readily adopted and only spread at all widely in China during the latter half of the 19th century. Indeed, vaccination in China was totally inadequate until the campaign mounted in 1950.

Epidemics of smallpox of great severity ravaged Tibet until 1940, when vaccination was first introduced. Smallpox is thought to have contributed significantly to the declining population of Tibet in the early 20th century.

Japan

The Japanese state came into being in about AD 650, when the population of the islands had reached approximately 3 million. Thereafter the population grew steadily—to 4.5 million in 1000, 9.75 million in 1300, 22 million in 1600 and about 30 million in 1700. There was then a check in population growth for a century and a half, with an explosion after 1850, when Japan was opened up to Western shipping and Western ideas, so that by 1900 the population had reached 45 million.

Smallpox had been repeatedly introduced into Japan from China and Korea ever since AD 585. At first it died out after each introduction but by the 10th century the disease was endemic. Numerous outbreaks occurred throughout the 10th century, with major epidemics recorded in the years 915, 925, 947, 974, 993 and 998. In 982 the "red treatment" (see box) was first described in *Ishinho*, a Japanese medical book. This practice later spread around the world and persisted in Europe and the USA down to the 20th century, as described by Hopkins (1983a). *Ishinho* also makes mention of special isolation hospitals for smallpox patients, several hundred years before the London Small-Pox and Inoculation Hospital was established in 1746.

During the 13th, 14th and 15th centuries Japan recorded 7 widely spaced epidemics of smallpox (1209, 1277, 1311, 1361, 1424, 1452 and 1454). Only 2 epidemics were recorded in the 16th century (1522 and 1550), but in the 17th century the country was more severely afflicted by outbreaks, during which the Japanese royal family was affected. The northern island of Hokkaido recorded an average of 1 epidemic of smallpox every 14 or 15 years during the 17th and 18th centuries.

At the end of the 17th century the Japanese distinguished 4 types of pox-like illnesses: *fooso* (variola), *fasuka* (measles), *kare* (chickenpox) and the "Portuguese disease" (syphilis) (Kaempfer, 1906). Strangely, the Japanese remained ignorant of the value of variolation until it was introduced from China in the mid-18th century, and as its population density increased Japan continued to suffer heavily from smallpox. Eventually, after

Customs of Mongols, as Affected by Smallpox

"From hereon, Mongols from the Inner Administration [i.e., Inner Mongolia] and from the Qalqas who are to inherit a rank, and have reached (legal) age [18 years], if they have once contracted smallpox, shall come to the capital to be installed, presented at court, and receive their succession. Those who have not yet contracted smallpox, shall proceed to Jeho [= Jehol, north of the Great Wall] to be installed, appear at court, and receive their succession." (Edict, 1784, quoted by Serruys, 1980.)

several unsuccessful attempts, vaccination was introduced into Japan in 1849, using crusts from vaccination lesions imported from the Netherlands East Indies. Between 1850 and 1860, smallpox vaccination clinics were opened all over Japan, and their success helped to erode the Japanese inhibition about Western learning. Smallpox epidemics continued, however, and there were several severe outbreaks in 1870. A new vaccine institute was established in Tokyo in 1874, and a compulsory vaccination act was promulgated in 1876.

Most accounts of the mortality associated with smallpox in the days before vaccination was available relate to statistics gathered in large cities. Suda & Soekawa (1983) have now provided a fascinating account of the impact of smallpox in rural Japan in the 18th and early 19th centuries. In 1795 a "virgin-soil" epidemic occurred in the village of Mine, on Hachijo-Jima, a small island south of Honshu. There were 1200 cases in a population of 1400 persons (85.7% morbidity) with 460 deaths (a case-fatality rate of 38.3%).

Using temple records, Suda & Soekawa were able to compute the smallpox mortality in the mountainous Hida district on Honshu Island, between the years 1771 and 1851. Smallpox was endemic in the district and neither variolation nor vaccination was practised. The smallpox mortality, as a percentage of total mortality in the whole population and in children under 5 years of age, is shown in Fig 5.3. Although the data relate to mortality, it is reasonable to assume that this reflects the morbidity. The periodicity of outbreaks is obvious, due presumably to the decrease and subsequent increase in the number of susceptible persons, with the periodic disappearance and reintroduction of smallpox. The brunt of the mortality was borne by children under 5 years of age, who constituted about 11% of the population but suffered well over 50% of the deaths from smallpox in epidemic years. In spite of the mortality due to smallpox, the population rose slowly from 2677 (calculated) in 1771 to 3127 (calculated) in 1851.

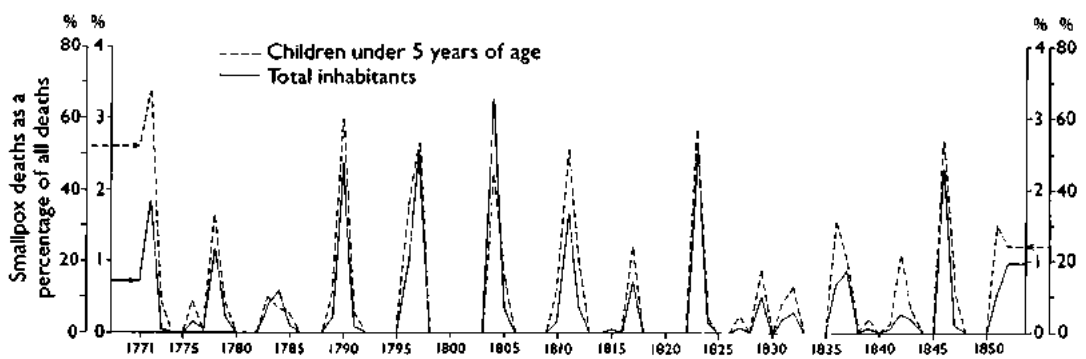


Fig. 5.3. The mortality from smallpox in the Hida district on Honshu Island, Japan, from 1771 to 1851. The population of the district rose from 2677 in 1771 to 3127 in 1851 (lowest 2535 in 1786; highest 3132 in 1834). The solid line indicates deaths due to smallpox as a percentage of all deaths. The broken line (and higher percentage figures) indicates deaths due to smallpox as a percentage of all deaths in children under 5 years of age. The total number in this age group rose from 310 in 1771 to 439 in 1851 (lowest 234 in 1838; highest 444 in 1850). (Data from Suda & Soekawa, 1983.)

The Red Treatment

Ishinbo was probably the first book to mention the existence of red cloth hangings in the rooms of smallpox patients. The practice persisted and in the 17th century a European doctor reported that Japanese physicians "... think it very material in the cure of smallpox to wrap up the patient in red cloth. When one of the Emperor's children falls sick of this Distemper, not only the room and bed are furnished with red; but all persons that come near the patient must be clad in gowns of the same colour" (Kaempfer, 1906). Red paper and red cloth were also hung around the beds of children with smallpox in China, India, Turkey and Asian Georgia; even in western Africa, the Yoruba god of smallpox, Sopona, was associated with the colour red.

In European countries the red treatment was practised from the 12th century onwards, and when he caught smallpox, King Charles V of France (reigned 1364–1380) was dressed in a red shirt, red stockings and a red veil. Queen Elizabeth I of England was likewise wrapped in a red blanket when she fell ill with smallpox in 1562, and similar treatments were applied to other European monarchs.

The red treatment was given scientific authority by Finsen, who claimed that the treatment of smallpox patients with red light reduced the severity of scarring, and later developed rules governing erythrotherapy (Finsen, 1901). It lingered on into the 1930s, although Ricketts & Byles (1904), Schamberg (1904) and others had declared it to be useless.

Indonesia and the Philippines

Two thousand years ago rice-growing Malay peasants were concentrated on the island of Java and the total population of the Malay Archipelago was about 2 million. Wet rice cultivation was introduced from India in about the 4th century and the population rose to 4 million by 1000 and 8 million by 1500. It continued to increase slowly until the European domination of the islands early in the 19th century, when the population soared from about 12 million in 1800 to 38 million in 1900.

The Philippine islands were even more sparsely populated initially, with only a few hundred thousand inhabitants by 1000, rising to half a million by 1500 and just over a million during the 17th century, when the islands were conquered by Christian Spaniards and Muslims from Indonesia. Thereafter, the population grew more rapidly, reaching 2.5 million by 1800 and 8 million by 1900.

Because of the frequent trading contacts between India and the larger islands of the Malay Archipelago from the 4th century onwards, there were repeated opportunities for the introduction of smallpox, but initially population concentrations were too small for the disease to become endemic. The Philippines were in frequent contact with China, but their population was even more sparse.

No written accounts of smallpox in the Philippines and Indonesia are available until the explorations of the Portuguese and Dutch seafarers in the 16th century, who reported that the disease was then known in both the archipelagos, but was endemic only on the larger islands. Elsewhere, importations of smallpox caused greatly feared epidemics, which occasionally originated from far away, as, for example, when a ship from Mexico carried smallpox to the Philippines late in the 16th century. Severe epidemics were reported in Sumatra in 1780–1783 and in Sarawak, on the island of Borneo, in the following century.

Vaccine virus arrived in Java from Mauritius in 1804, and vaccination was employed from 1816 onwards. However, supplies often failed because regular arm-to-arm vaccination was not begun until 1856. A central vaccine institute was established in Jakarta at the end of the 19th century.

Further north, smallpox was recorded in Penang in 1805, and was introduced into Singapore shortly after it was founded in 1819. Because of commercial traffic with India and China, Singapore, while too small to maintain endemic smallpox, was subject to repeated epidemics due to importations, with notable outbreaks in 1838, 1849–1850, 1859–1860, 1899–1900, 1902–1903 and 1910–1911.

SMALLPOX IN EUROPE BETWEEN 1000 AND 1900

Smallpox had occurred in Europe as an occasional epidemic following importations before the end of the 1st millennium of the Christian era, by which time it was established as an endemic disease on the southern and western fringes of the continent, but not in central and northern Europe. The movement of European Christians to and from south-western Asia in the course of the Crusades during the 11th and 12th centuries helped to spread smallpox in Europe, and "entirely unambiguous" statements about the prevalence of smallpox in Europe date from that time (Hirsch, 1883). Some dramatic episodes were recorded shortly after this; for example, in 1241 the first epidemic among the "virgin-soil" inhabitants of Iceland killed some 20 000 of its total population of about 70 000, to be followed by other severe epidemics in 1257 and 1291.

The steady growth of population in Europe, particularly in the north-west, from a low figure of about 26 million in the 8th century to some 80 million by the beginning of the 14th century, was interrupted by the Black Death, which reduced the population by more than 25%. Thereafter, it began to increase steadily again—from 80 million in 1500 to 100 million by 1600—but there was a set-back in 1620–1650 associated with the Thirty Years War and several severe outbreaks of plague. The 18th and early 19th centuries saw very rapid population growth from 140 million in 1750 to 250 million by 1845.

By the 15th century smallpox had become endemic in many parts of Europe and was recorded as a disease of children in Paris. However, it does not appear to have been quite as severe as it became in the 17th and 18th centuries. Reasonably good mortality records are available for Italy and Spain at this time, but they give little prominence to smallpox (Carmichael, 1983). Perhaps the strains of virus then circulating, although not as mild as variola minor as seen in the 20th century, were somewhat less virulent than classical variola major. Endemicity was not established in the outlying islands and both Iceland and Greenland occasionally suffered epidemics that caused numerous deaths in all age groups (Steffensen, 1977).

At the end of the 15th century venereal syphilis was recognized as a "new" exanthematous disease, which the French called *"la grosse vérole"* to distinguish it from variola, which became *"la petite vérole"*. The English followed suit; "pox" becoming the "small pox" and syphilis the "great pox"—the epithet "great" denoting the larger size of the primary and tertiary lesions and, in addition, conveying the notion that it affected adults whereas smallpox was largely a disease of children.

By the 16th century smallpox was well established over most of Europe, except possibly Russia, and as the population increased and became urbanized epidemics occurred more and more frequently, and were better recorded, especially when they affected the royal houses of England, France and Spain. For the first time, important scientific works on infectious disease emerged from Europe, and Girolamo Fracastoro's classic treatise on communicable diseases, *De Contagione et Contagiosis Morbis*, was published in 1546. He noted that diseases such as smallpox were specific contagions that could spread from person to person directly or via fomites, or even through the air. He also commented on the fact that smallpox was primarily a disease of children, as had al-Razi 600 years earlier. In Spain, the presence of smallpox at this time was of particular importance because it provided the source of the shipboard infections that the conquistadors were to spread to the New World.

The 17th century was a period of turmoil in Europe, with constant military activity, the rapid growth of cities and the burgeoning of intellectual activities in the urban class. Academies were established and scientific journals published. Smallpox succeeded plague, leprosy and syphilis as the continent's foremost pestilence. The great English physician Thomas Sydenham (1624–1689), like Ko Hung and al-Razi long before him, clearly distinguished smallpox from measles and observed the different prognoses of patients with confluent and discrete smallpox rashes. A pandemic of smallpox that swept much of Europe and the Near East in 1614 was important because it was probably responsible for the first importation of smallpox into the English and French colonies in North America. At this time also smallpox was established in Russia and was soon carried from Moscow to Siberia, where devastating epidemics occurred in previously unexposed populations.

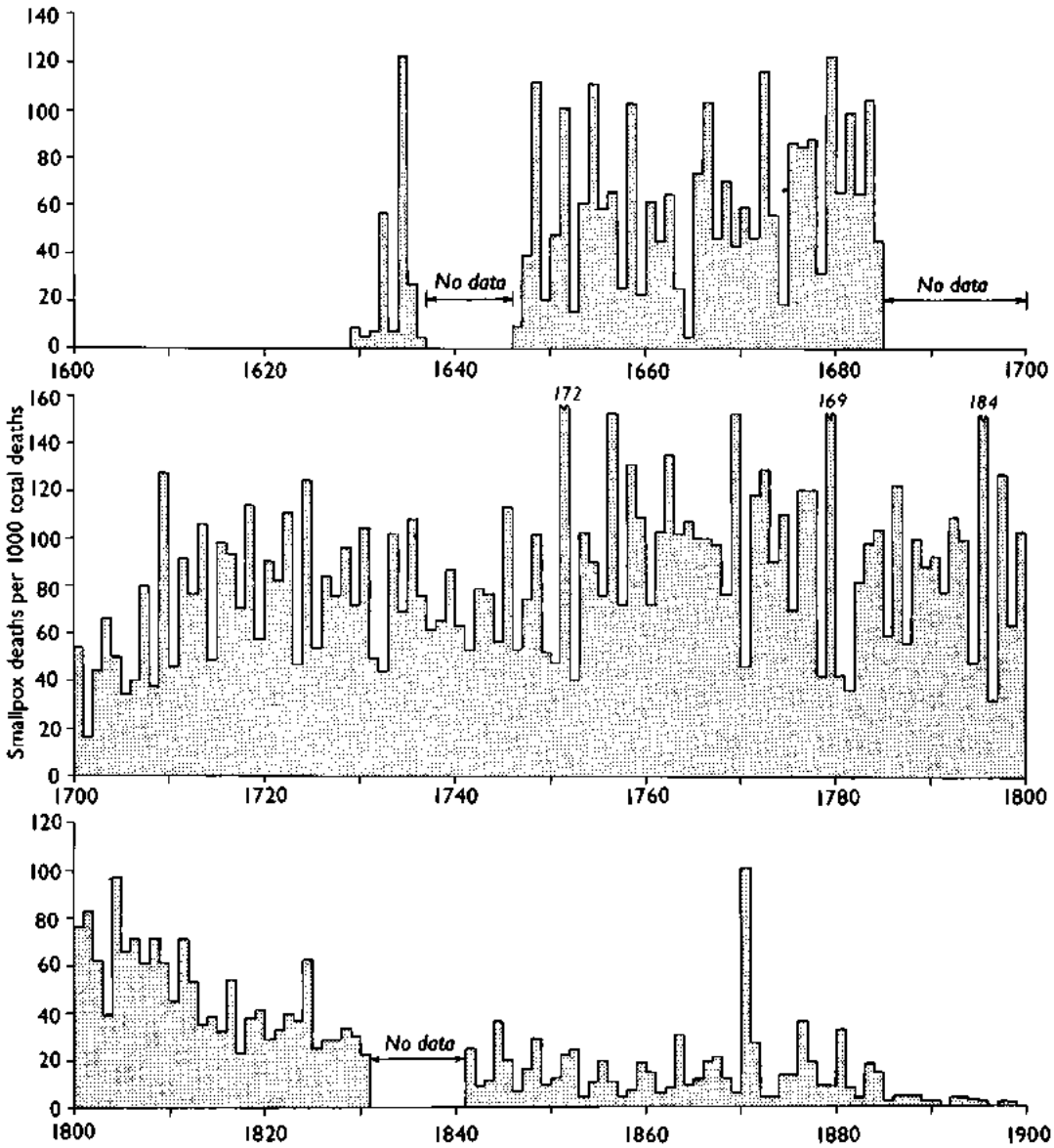


Fig. 5.4. Deaths from smallpox per 1000 deaths from all causes in London, from 1629 to 1900. (Data from Guy (1882) and the Registrar General's Statistical Review of England and Wales.)

An important innovation at this time was the introduction of statistical records. Parishes in London began registering church burials by cause of death, and from 1629 onwards "Bills of Mortality" were published in London (Fig. 5.4).

The authorities in Geneva had started keeping records of deaths from smallpox by age groups from 1580 (Perrenoud, 1980), and in 1680 the Tsar initiated a reporting system in Moscow. From this time onwards, also, the infection of members of Europe's royal houses had dramatic effects on the succession in several countries, a feature of smallpox in history that is well described by Hopkins (1983a).

Even greater devastation occurred during the 18th century, affecting the general population and royalty alike. The London Bills of Mortality, incomplete though they were, record the increasing impact of smallpox in England (Fig. 5.4). Severe epidemics occurred in Paris in 1719 and 1723, and in the 80 years before 1775 smallpox killed Queen Mary II of England, Emperor Joseph I of Austria, King

Luis I of Spain, Tsar Peter II of Russia, Queen Ulrika Eleonora of Sweden and King Louis XV of France; this doubtless influenced royalty in several countries to promote the practice of protective inoculation (variolation). By the middle of the 18th century variolation was having an ameliorating effect on the mortality of smallpox among the well-to-do in Great Britain, the Netherlands and Switzerland. As with vaccination in later centuries, its popularity waned when smallpox was less common and was revived by epidemics, such as the large epidemic in Great Britain in 1752. Variolation remained unpopular in France, Italy, Spain and Sweden, all of which experienced severe outbreaks. In Russia, however, Catherine II, affected no doubt by the experience of smallpox in her own household and by the tragedies in the Hapsburg families, commissioned an Englishman, Thomas Dimsdale, to inoculate her and thus popularized variolation in Russia, which was still suffering from recurrent severe epidemics of smallpox, especially in Siberia and Poland.

The effects of smallpox during the latter part of the 18th century can be appreciated by an examination of the data assembled by Hopkins (1983a). During the last 2 decades of the 18th century, smallpox killed over 36 000 persons in London, and an equal number in Glasgow. This constituted almost 1 out of every 10 deaths in London, and nearly a fifth of all the deaths in Glasgow in that period. In British towns, 9 out of every 10 persons who died of smallpox were under 5 years old.

Smallpox was always present in Great Britain's densely populated large cities, even between epidemics, whereas in the more sparsely populated countryside it commonly appeared only in epidemics, separated by smallpox-free intervals of several years. For young adults from these rural areas who had previously escaped infection, smallpox was one of the most serious risks they faced in the big cities.

In continental Europe also, smallpox was still very destructive. In Sweden, major epidemics in 1779 and 1784 killed over 27 000 persons in those two years alone. Rosen von Rosenstein, a Swedish physician, reported that smallpox killed 10% of all Swedish infants each year. In Russia, Sir Alexander Crichton, the Tsar's British physician, reported that one-seventh of all Russian infants died of smallpox each year. And in France also, de La Condamine claimed that 1 out of every 10 persons born in that country died of smallpox. Berlin recorded 6 smallpox epidemics between 1766 and 1795, each of which carried off about 1000 inhabitants. The Berlin epidemic of 1795 was thought to have been initiated by spread from freshly inoculated persons, and epidemics in Weimar (1788) and Hamburg (1794) were attributed to the same cause. In Vienna, over 16 000 persons were infected during an outbreak in 1790, of whom about 1500 died. Iceland had epidemics in 1707 and 1786.

In 1796, the year of Jenner's discovery of the protective value of cowpox, smallpox killed over 3500 persons in an epidemic in London. Throughout Great Britain and Ireland, the disease claimed an estimated 35 000 more lives that year. In the German states, over 65 000 deaths were attributed to it. Europe (excluding Russia) was losing over 400 000 citizens each year through deaths from smallpox, which also was responsible for more than a third of all the cases of blindness in Europe.

With Jenner's publication of his discovery of the protective effect of inoculation with cowpox virus (see Chapter 6), vaccination spread with remarkable speed, in sharp contrast to the slow adoption of variolation in most European countries. It was soon practised on such a large scale that it altered the pattern of smallpox, the incidence of which declined and remained at relatively low levels for the first few decades of the 19th century (Fig 5.4). Such epidemics as did occur were less severe. In Sweden extensive vaccination reduced the number of reported deaths from smallpox from about 12 000 in 1800 to 11 in 1822 (see Chapter 6, Fig. 6.1), and in Denmark not a single case was recorded between 1811 and 1818. Nevertheless, an estimated 8 million Russians suffered from smallpox between 1804 and 1810, of whom 827 000 died. In addition to epidemics in various European cities, smallpox pandemics occurred in 1824–1829 and 1837–1840 which affected nearly all of Europe. The reasons for this resurgence were complex. At that time vaccination was a cumbersome procedure involving arm-to-arm inoculation, and, with the lower incidence of smallpox, enthusiasm for vaccination declined. Another reason was probably the failure to appreciate the fact that a single vaccination did not give lifelong protection. This problem was overcome when revaccination was introduced in Germany in 1829, although it was not adopted by the

British army until 1858 and by the civilian population much later than that.

The Franco-Prussian War of 1870–1871 was associated with severe outbreaks among the poorly vaccinated civilians of France and Prussia (Prinzing, 1916). The Prussian army of 800 000 men, revaccinated every 7 years, suffered only 8463 cases of smallpox, with a case-fatality rate of 5.4%, whereas in the unvaccinated French army there were 125 000 cases, with a case-fatality rate of 18.7%. As expected, smallpox spread beyond the belligerent states to the rest of Europe, and it was estimated that at least half a million Europeans died of smallpox in the pandemic triggered by the Franco-Prussian War (Rolleston, 1933). One consequence was legislation to enforce vaccination and revaccination in many countries of Europe, but in some countries these efforts were countered by violent antivaccination movements—notably in Great Britain—based primarily on the principle that compulsory vaccination was an infringement of personal liberty. The century closed with smallpox still endemic in every country of Europe, but with more hope for the future because of improvements in vaccine quality and production methods and in the public health infrastructure.

THE SPREAD OF SMALLPOX BY EUROPEAN EXPLORERS AND COLONISTS

Up to about the 15th century smallpox appears to have been confined to the Eurasian land mass and a few adjacent countries: those of northern and western Africa and the Horn of Africa, Japan, and Ceylon and the Malay and Philippine archipelagos. Arab traders and slave-traders had introduced it into the coastal areas of eastern and western Africa, but most of central and southern Africa was probably free of the disease. The great explorations and subsequent migrations of Europeans to the Americas, Africa and Australia in the 15th–18th centuries opened up those entire continents to the fatal impact of the advanced technologies and infectious diseases of Europe. Some European conquests owed a good deal of their success to the effects of disease on the indigenous peoples, especially smallpox in the Americas. Fig. 5.5 illustrates the pattern of introductions of smallpox to continents outside the Eurasian land mass. Subsequent sections of this chapter elaborate on the history of smallpox in these newly invaded continents -Africa, the Americas and Australia.

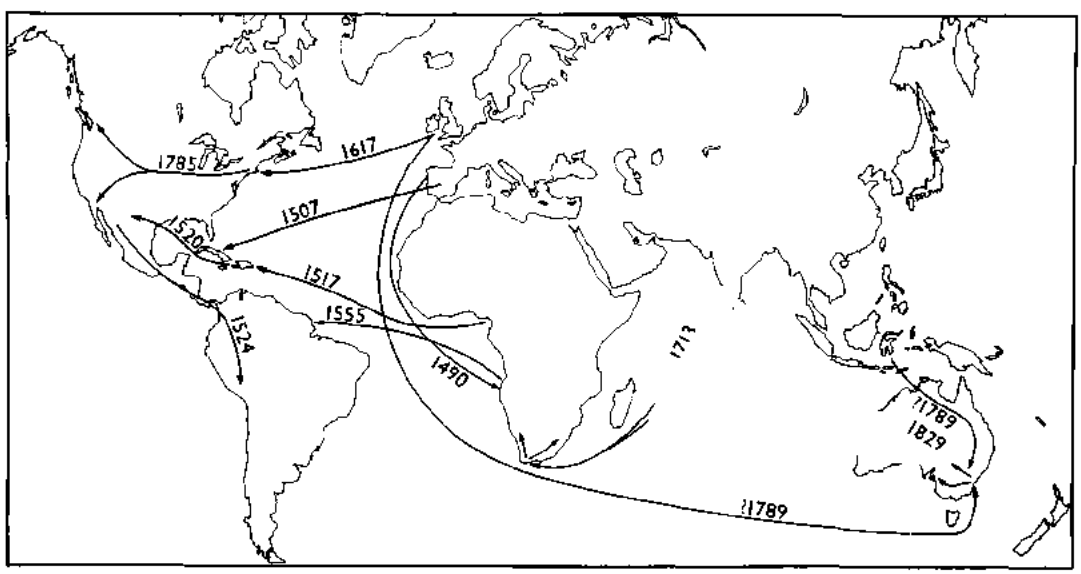


Fig. 5.5. The spread of smallpox to the Americas, South Africa and Australia with European exploration and colonization. It is not known whether the outbreaks among Australian aborigines in 1789 were caused by the transmission of the disease by ship from Great Britain or spread from islands of the East Indies to northern Australia.

SMALLPOX IN AFRICA BETWEEN 1000 AND 1900

The vast continent of Africa is relatively sparsely inhabited now, and its population was far smaller a thousand years ago. The desert area of the Sahara, then as now, separated the countries of the Mediterranean littoral and the Nile valley state of Egypt from sub-Saharan Africa, in which the great rain forests of the Niger and Zaire basins and the Kalahari desert in the south were largely uninhabited (Fig. 5.6).

Africa is racially and culturally complex. By AD 1000 the Bantu-speaking Negroes, who originated in western Africa, had spread throughout central and eastern Africa and were probing southwards. The aboriginal inhabitants of central and western Africa were reduced to a minority living in the dense tropical forests, and the Bushmen were confined to southern Africa and the Kalahari desert. The population south of the Sahara probably numbered about 30 million, mostly Negroes.

In the north the earliest presumptive evidence of smallpox anywhere in the world is in Egyptian mummies, over 3000 years old. Later, smallpox swept along the North African coast at the time of the great expansion of Islam in the 8th century, and from that time onwards remained endemic in these Mediterranean lands.

Apart from areas of western Africa near the Gulf of Guinea, the mediaeval African countries developed in the interior of the continent, in the grasslands south of the Sahara, the central uplands of the Rift Valley and south to Zimbabwe. Commerce between Egypt and the north-eastern countries (present-day Ethiopia, Somalia and the coastal part of Kenya) and the countries of south-western Asia to the north was active from ancient times. One of the earliest records of a pestilence that may have been smallpox was, as already noted in this chapter, associated with the "Elephant War" in AD 568, when Ethiopian troops besieged Mecca and were decimated by disease, which they carried back to Africa.

Since there were Arab colonies in the port towns along the eastern African coast as far south as Mombasa, and Arabs traded as far afield as India and China, it is likely that smallpox was periodically imported into these coastal towns, perhaps as early as the 13th or 14th century. But no written records are available earlier than those of the 16th century, when Portuguese traders replaced Arab merchants. The coastal towns were sometimes raided by tribes from the interior, and in 1589, after one such raid along the coast of Kilwa and Mombasa, a severe epidemic of smallpox affected all age groups among the African inhabitants but spared all the Portuguese except the young children.

The populous countries of western Africa were connected by caravan routes to Nubia and Ethiopia in the east and the countries of the Mediterranean littoral to the north. After the arrival of Islam in the 11th century, trading relationships were strengthened and pilgrims travelled to Mecca. It is likely that smallpox was introduced into some of these relatively densely populated western African kingdoms from the 11th century onwards, but there are no European records about smallpox in western Africa until the 17th century, when the disease was apparently widespread, variolation appears to have been practised, and a god of smallpox was an established member of the indigenous pantheon of some tribes (Plate 5.5). Smallpox had probably been endemic there for some centuries, many years before the slave trade to the Americas was established in the 16th century.

The slave trade provided excellent conditions for spreading smallpox, and since raiders penetrated deep into the interior the overland caravans carried the disease far and wide in central Africa. No contemporary records exist of these incursions, but later European explorers recorded the devastating effects of smallpox that they found along every caravan route. Those who failed to contract smallpox on the trek to the coast were liable to be infected while awaiting shipment or on board ship, and there are numerous records of smallpox at the coastal camps and in the slave ships during the 17th and 18th centuries. Indeed, such shipments were a perceived threat to the colonists in the Americas. On the east coast, also, slave ships carried smallpox, as recorded in 1729 in a ship travelling from Madagascar to Réunion.

The Portuguese established a settlement at Luanda, Angola, in 1484, and probably introduced smallpox into the area shortly after that. Over the next 2 centuries smallpox and the slave trade combined to take a terrible toll of the population.

Southern Africa was free of smallpox when the Dutch settled in Cape Town in 1652. At this time the only indigenous inhabitants were Bushmen and Hottentots, but the Ban-

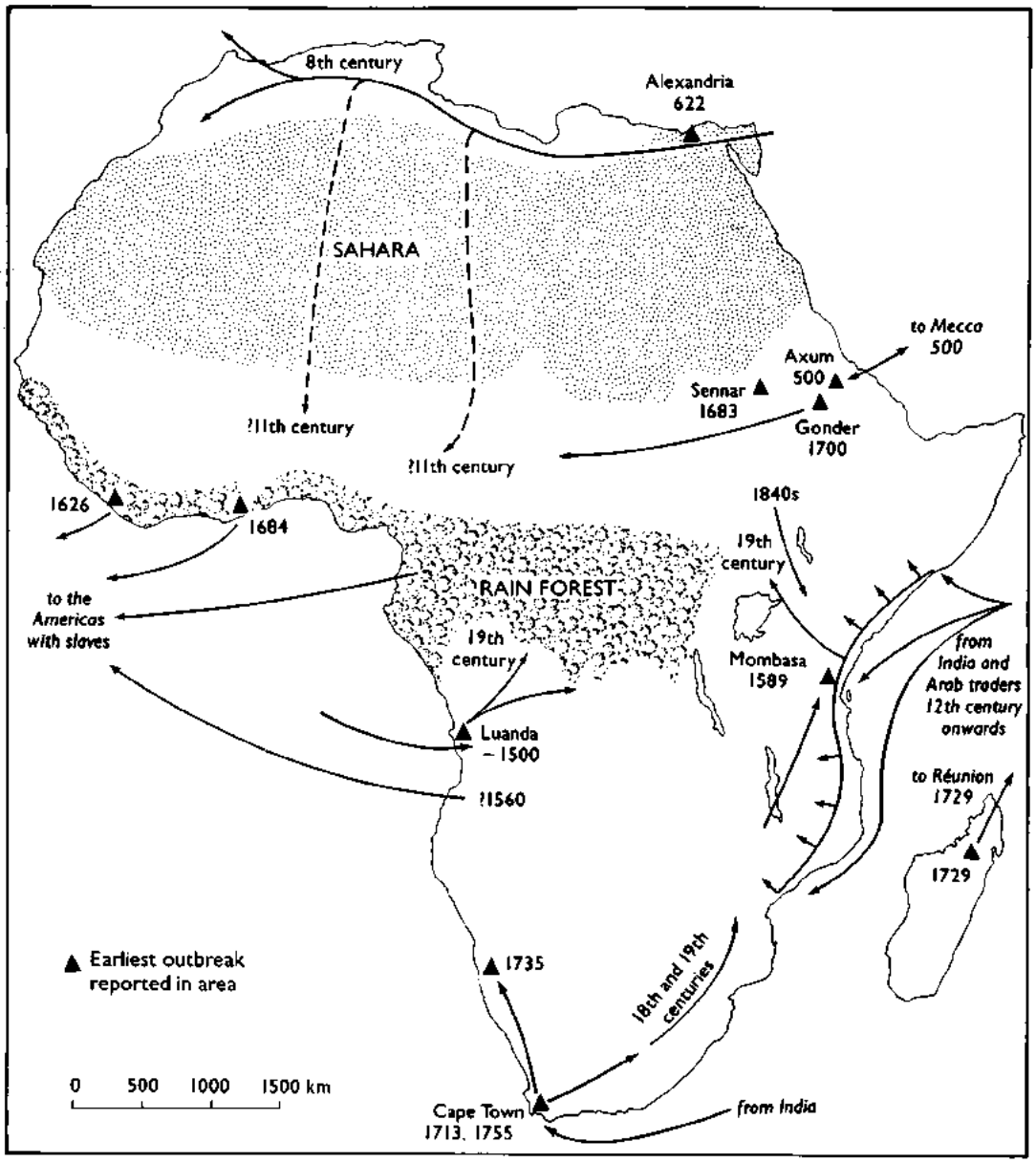


Fig.5 6. Spread of smallpox to Africa and within the African continent. Endemic smallpox was established in the Maghreb during the Islamic conquests in the 8th century and probably spread from there along the trade routes across the Sahara to the dense populations of western Africa during the 11th and 12th centuries. Further south in western Africa smallpox was not imported until the Portuguese occupation in the 15th and 16th centuries. Thereafter it was exported from western Africa to the Americas. On the eastern coast, smallpox was imported periodically from India via Arab and Indian traders. Another focus was established in southern Africa after importations in 1713 from India and 1755 from Ceylon. The interior of the continent was probably smallpox-free until the 19th century. (Based on Hopkins, 1983a.)

tus were already migrating southward from Zimbabwe. In 1713 smallpox was imported into South Africa with a ship that was returning from India and docked at Cape Town. Although there were no active cases aboard, the virus was taken ashore in laundry. In the ensuing outbreak the white population suffered severely, nearly every family being affected. Many of the Dutch adults were immune because of smallpox contracted during their childhood, but the Hottentots were totally susceptible, and very large numbers of

them died, whole clans being wiped out. Smallpox did not become endemic, however, and a second outbreak followed an importation into Cape Town from Ceylon in 1755. Again, although the whites suffered severely, with over 1000 deaths between May and October, the Hottentots were even more severely devastated. The disease spread among the Hottentots and Bushmen as far as the Kalahari desert, and wiped out several Hottentot tribes. Yet a third outbreak occurred in 1767, introduced on this occasion by a Danish ship from Europe. The European settlers had by this time learned of the value of variolation and suffered only 179 deaths among some 2000 cases, but the remnants of the Hottentots and the Bantu tribesmen, who were by then in the vicinity, suffered much more severely.

Although the Atlantic slave trade was curtailed from the early 19th century onwards, Arab slavers continued to operate in eastern Africa and carried smallpox from Mozambique to Cape Town in 1812, and to Mauritius in 1840. Slave ships intercepted by the British navy sometimes brought smallpox into African ports then free of the disease—as occurred in 1840, when a captured slave ship brought smallpox again to the Cape Colony, starting another outbreak, which killed over 2500 of the inhabitants.

In the 19th century the Arab slave trade expanded from the east coast ports into central Africa. Smallpox was brought into Uganda by slave caravans in the 1840s. Although there may have been earlier introductions by ivory hunters, the populations were too sparse to support endemic smallpox. The increased commerce and population movements of the 19th century thus brought smallpox to hitherto unaffected populations, on which it wrought extreme havoc. Mortality rates of 80% were reported among the Griqua people in 1831, and as late as 1899 smallpox almost exterminated some tribes in northern Kenya. A similar pattern was observed as central Africa was opened up to European trading from the west, and some parts of the eastern Zaire river basin were completely depopulated.

In the meantime smallpox continued to be a severe endemic disease in coastal towns and in northern Africa. In addition, 6 epidemics were recorded in Ethiopia and the Sudan in the 19th century—in 1811–1813, 1838–1839, 1865–1866, 1878–1879, 1885–1887 and 1889–1890. In western Africa, also, smallpox continued to take a toll of lives and to affect military campaigns, as in the Ashanti Wars in the 19th century. In Angola, an epidemic that started in 1864 affected about one-third of the Angolan population, killing over 25 000 persons, and helped to shift the balance of population towards the south.

"The variola epidemic by mid-1864 was on the rampage. It spread inland to the east with many caravans of trade, and spread south along the coast by contact with vessels in the ports. Two of the most famous explorers of Central Africa residing in Angola died as a result of this epidemic in 1864 ... The negroes fled in all directions to avoid the epidemic ... entire populations would migrate from their villages ... Luanda was on the verge of anarchy as people died in great number ... Great quantities of wax, ivory, gum, and copper, indeed the sinews of trade, stayed in piles along the roads and paths or abandoned in heaps at such inland stations as Malanje." (Wheeler, 1964.)

Variolation antedated European colonization of western Africa. It was practised in southern Africa from the mid-18th century and was known in all regions of Africa from the early 19th century (see Chapter 6), but nowhere was it used as a method of protecting communities—only individuals. In some parts it was feared as a mechanism for the spread of smallpox, especially in western Africa, where the *fêticheurs*, who by tradition carried out the inoculations, stood to profit from the practice.

Finally, the earliest accounts of a mild form of smallpox, now called variola minor, are those describing "kaffir-pox", or "amaas", in South Africa (see Chapter 6).

SMALLPOX IN THE AMERICAS BETWEEN 1507 AND 1900

The Americas were first colonized by migrants from Asia who crossed the northern land (ice) bridge over the Bering Strait some 20 000 years ago. Before Columbus "discovered" America in 1492 these people had spread throughout both North and South America, to the very southernmost tip of the continent in Tierra del Fuego. Two thousand years ago the total population of the Americas was probably about 5 million; it had doubled by AD 1000 and reached approximately 25 million by 1500. In Mexico the Aztec empire embraced an estimated 8 million subjects, somewhat more than did the Inca empire in Peru. Tenochtitlán and Cuzco were great cities, with large populations. Along the

eastern seaboard of North America, in the Caribbean, in southern Mexico and Central America, Venezuela, Colombia and northern and eastern Brazil, there were semi-agricultural tribes who added another 5 or 6 million to the continental total. In addition, there were about 3 million hunters and food-gatherers roaming the immense and empty lands of central and western North America, the tropical jungles of Brazil and the desolate wastes of southern Argentina (Fig. 5.7).

These large populations, city-dwellers and agriculturists alike, were free of the familiar communicable diseases of Europe. When smallpox was introduced into Mexico and Brazil by the Spanish and Portuguese invaders and into North America by the British and French, its impact was catastrophic. Since these episodes differed in many respects it is convenient to consider them separately.

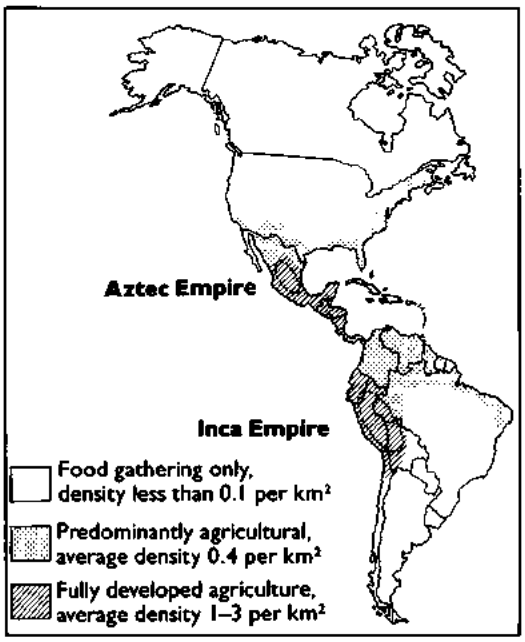

Aztec Empire
Inca Empire
Food gathering only, density less than 0.1 per km²
Predominantly agricultural, average density 0.4 per km²
Fully developed agriculture, average density 1–3 per km²

Fig. 5.7. Agricultural development and population densities in the Americas at the time of the European invasions. (Based on McEvedy & Jones, 1978.)

The Spanish and Portuguese Colonies

The first occurrence of smallpox in the Western Hemisphere was on the island of Hispaniola in 1507, following an importation from Spain. The epidemic which followed exterminated whole tribes, but eventually died out. Most subsequent importations into the Caribbean islands, Mexico and Brazil were associated with the African slave trade, which began in about 1503. In 1517 an outbreak occurred among African slaves in the mines of Hispaniola and spread rapidly to the Amerindian population of that island, killing about one-third of them. Smallpox spread to Cuba in 1518 and Puerto Rico in 1519, where over half the native population succumbed to the disease.

In 1519 Cortés and his followers sailed from Cuba to Mexico and arrived in November in Tenochtitlán, whose size and splendour amazed them. Jealous of Cortés' good fortune, the Governor of Cuba sent another expedition under Narváez to replace Cortés. Narváez landed near present-day Vera Cruz in April 1520, and his entourage included an African slave who had smallpox. The result (Plate 5.3B) was described by a Spanish friar, who arrived in Mexico in 1525:

"... at the time that Captain Pánfilo de Narváez landed in this country, there was in one of his ships a negro stricken with smallpox, a disease which had never been seen here. At this time New Spain was extremely full of people, and when the smallpox began to attack the Indians it became so great a pestilence among them throughout the land that in most provinces more than half the population died; in others the proportion was little less. For as the Indians did not know the remedy for the disease and were very much in the habit of bathing frequently, whether well or ill, and continued to do so even when suffering from smallpox, they died in heaps, like bedbugs. Many others died of starvation, because, as they were all taken sick at once, they could not care for each other, nor was there anyone to give them bread or anything else. In many places it happened that everyone in a house died, and, as it was impossible to bury the great number of dead, they pulled down the houses over them in order to check the stench that rose from the dead bodies so that their homes became their tombs. This disease was called by the Indians 'the great leprosy' because the victims were so covered with pustules that they looked like lepers. Even today one can see obvious evidences of it in some individuals who escaped death, for they were left covered with pockmarks." (Foster, 1950.)

From the coast the disease spread inland, reaching the Valley of Mexico in September and shortly after that the capital, Tenochtitlán. The epidemic which followed was catastrophic for the Amerindians and assured the military success of Cortés and his conquistadors. The Aztecs' loss of chiefs and fighting men was serious enough, but the observation

that the Spaniards were immune (from childhood infection in Spain, into which country the Moors had introduced the disease in the 8th century) completed their demoralization. Estimates of the number of deaths vary. Some say that half the population of Mexico died within 6 months; other estimates put the population at 25 million before the conquest and 16.8 million 10 years later. At least half of the Aztecs who caught smallpox died of it. From Mexico, the disease spread south into Guatemala and Yucatán, which may have been ravaged by an earlier outbreak in 1515, and greatly decreased the formerly dense population of the Yucatán Peninsula.

Hearing of the riches of the Inca empire far to the south, the Spaniards decided on further expeditions. Before these could be mounted, smallpox reached the land of the Incas in about 1524–1527, killing some 200 000 of the 6 million inhabitants. Just as important as this widespread devastation, from the point of view of the subsequent Spanish conquest, was the fact that the Inca emperor and his designated heir also died of smallpox, and a disastrous civil war broke out for the succession. These events so weakened the Incas that Pizarro and his small band entered Cuzco in triumph in 1533, to be followed by further epidemics of smallpox.

From then on the history of the Amerindians in the Caribbean islands, Mexico, Central America and Peru is punctuated with epidemics of smallpox that were said to kill "hundreds of thousands"; in 1576, as many as 2 million Mexican Indians were alleged to have died. Colombia and Venezuela were invaded, with the same disastrous consequences for the natives, and Spanish soldiers introduced smallpox into Chile for the first time in 1554, and again in 1561 and 1591. By this time there were many locally born "Spaniards" who had not been exposed to smallpox and some 300 died, as well as countless Indians.

In 1506, by Papal decree, the New World had been divided between the Spanish and the Portuguese. What is now Brazil was the principal Portuguese colony, and it was soon struck by smallpox. The first introduction, in 1555, followed the establishment of a French Huguenot settlement, to be followed by fresh introductions by African slaves in 1560, and from Portugal in 1562 and 1563. The last epidemic spread along the coast and along the rivers into the Indian populations of the forested interior and was said to have killed more than half the natives of the state of Bahia.

By 1588, epidemics of smallpox erupted over the whole South American continent, and subsequently wave after wave of epidemic smallpox decimated the native populations. The resulting depopulation had as important an influence on the history of South America as the supportive role of smallpox in the conquest of Mexico and Peru. No part of the continent was spared—not even the interior of Brazil, whose inhabitants were exposed through the enthusiasm of Jesuit missionaries for converts. As late as 1660, after the Jesuits had established missions along the banks of some of the great rivers, where some 100 000 Indians had been assembled, a smallpox epidemic killed 44 000 of them, to be followed by another 9 years later, which claimed 20 000 victims.

Variolation was introduced into the colonies in 1728 by missionaries from Portugal, but it was not extensively practised. Smallpox continued almost uncontrolled throughout the 18th century, occurring as an endemic disease with epidemics every few years. The last and best-described epidemic, before vaccination became available, occurred in Mexico in 1797. It was notable in that over 60 000 inoculations with variola virus were performed during the epidemic. While protecting most of those inoculated, the practice may have contributed to the spread of smallpox. The changed nature of the population was evidenced by the fact that three-quarters of the estimated 100 000–150 000 cases were in persons less than 20 years old. The case-fatality rate among 3300 variolated individuals was 3.5%, compared with 18.5% among 58 000 naturally acquired cases of smallpox.

The early years of the 19th century were marked by successful struggles for independence throughout South America. Brazil proclaimed its independence from Portugal in 1822, and in 1824 Spanish rule was ended in Peru, the last Spanish colony. From as early as 1798 attempts were made to introduce Jenner's vaccine, of which the most dramatic was the Balmis-Salvany Expedition of 1803–1806, ordered by King Carlos IV of Spain (Smith, 1974), in which 20 orphans were used for successive arm-to-arm transfer of the vaccine during the voyage. However, smallpox continued in all parts of the continent throughout the 19th century, as an endemic disease punctuated periodically by epidemics, especially in the densely populated port cities.

The most profound demographic effect of European conquest, achieved in large part by smallpox, was on the native populations of the islands of the Caribbean, where the population was virtually wiped out, to be replaced by African slaves and Spanish conquerors and their descendants. On the mainland the size of the Amerindian populations of the Aztec and Inca empires ensured their survival; over half the present populations of Mexico, the countries of Central America, Bolivia, Colombia, Ecuador, Paraguay, Peru and Venezuela are of Amerindian stock; elsewhere in North and South America they constitute a small minority.

North America

In contrast to the urban civilizations of Mexico and Peru, the vast area of America to the north of Mexico was occupied by an estimated 3 million Amerindians, living as hunter-gatherers, and practising a primitive type of agriculture along the eastern seaboard. It was almost a century after the invasion of the Caribbean, Mexico and South America by the Spanish and Portuguese that the east coast of North America was colonized by settlers from France, Great Britain and the Netherlands. Smallpox followed the settlers, the first epidemic in 1617–1619 killing many of the Indians on the Massachusetts coast, thus clearing a place for the settlers who arrived from Plymouth in 1620.

Further outbreaks of smallpox followed, with devastating effect as they spread inland, for the Indians were without immunity and their way of life was disrupted by the epidemics, which affected persons of all ages. Some colonists, being themselves immune from childhood infection, actively fostered the spread of smallpox among the native North Americans (Stearn & Stearn, 1945). The severity of the disease and its spread were exacerbated by the reaction of the Indians to the disease. Terror-stricken relatives of victims fled, carrying the infection with them.

As Crosby (1976) points out:

"... the British tended to drive the Indians away, rather than ensnaring them as slaves and peons, as the Spaniards did, with the result that many of the most important events of aboriginal history in British America occurred beyond the range of direct observation by literate witnesses... Even so, the surviving records for North America do contain references—brief, vague, but plentiful—to deadly epidemics among the Indians, of which we shall cite a few of the allegedly worst. During the 1630s and into the next decade, smallpox, the most fatal of all the recurrent Indian killers, whipsawed back and forth through the St Lawrence–Great Lakes region, eliminating half the people of the Huron and Iroquois confederations. In 1738 smallpox destroyed half the Cherokees, and in 1759 nearly half the Catawbas. During the American Revolution it attacked the Piegan tribe and killed half its members. It ravaged the plains tribes shortly before they were taken under United States jurisdiction by the Louisiana Purchase, killing two-thirds of the Omahas and perhaps half the population between the Missouri River and New Mexico. In the 1820s fever devastated the people of the Columbia River area, erasing perhaps four-fifths of them. In 1837 smallpox returned to the plains and destroyed about half of the aborigines there."

Not all the settlers were immune, so that smallpox was not, for them, an unmixed blessing. At this time smallpox was endemic in all the larger European cities, with epidemics occurring at intervals of a decade or so. The towns in North America were still too small to support endemic smallpox, so that epidemics occurred whenever the disease was imported at a sufficiently long interval after the last outbreak for enough susceptible persons to have accumulated within the population. The disease usually arrived by ship at the ports on the eastern seaboard, either with settlers from Great Britain or, later, with slaves from Africa. Boston suffered major epidemics in 1636, 1659, 1666, 1677–1678, 1689–1690 and 1697–1698, and there were outbreaks in New York, Jamestown (Virginia), Charleston (South Carolina), and elsewhere. As well as causing substantial numbers of deaths among the settlers, especially those born in the colonies, it disrupted life in the fledgling cities.

One consequence of the obvious association of smallpox outbreaks with cases on ships was the imposition of quarantine measures on ships with infected persons aboard. This was initiated in Boston in 1647, probably for yellow fever, and was later extended to other parts of the colonies. It proved useful in preventing the importation of smallpox. On land, also, attempts were made at various times from about 1670 onwards to prevent smallpox from spreading from Indians to the colonists, and among the colonists, by local quarantine and isolation. Another consequence of the difference in the endemicity of smallpox in the colonies and in Great Britain

Smallpox and Educational Institutions

"When a French visitor ... visited William and Mary College in 1702, he was surprised to find as many as forty students there ... he learned that wealthy parents who formerly had sent their sons to England now preferred the intellectual crudities of a colonial education to the perils of the English smallpox. The Rev. Hugh Jones, in 1724, observed that more Virginians would have been given an English education 'were they not afraid of the Small-Pox, which most commonly proves fatal to them'." (Boorstin, 1958.)

was that many young colonials, who had been brought up in smallpox-free areas, contracted the disease when they went to Great Britain for further studies, or else refused to take the risk and remained on their side of the Atlantic. Indeed, the risk of contracting smallpox in Great Britain was one of the reasons for founding colleges and universities in the colonies.

In the latter part of the 17th century smallpox and military activity interacted in the wars between Great Britain and France, each with Indian allies, in what was to become Canada. With the growth of populations in the port cities on the Atlantic coast and on the banks of the St Lawrence river during the 18th century, smallpox became more frequent and the outbreaks more intense; for example, an epidemic in Quebec City in 1702–1703 was said to have killed nearly a quarter of the inhabitants (Heagerty, 1928). Severe outbreaks occurred in Boston, New York, Philadelphia, and the State of New Jersey, and at the approach of such epidemics many of the townspeople fled to the country. In both New England and the South, smallpox broke the resistance of the Indians to the white invaders, and as white settlement moved westwards it was accompanied by smallpox, to which the local Indians had no resistance. A few of these 18th century epidemics among the Indians were probably initiated, or at least fostered, by whites. The most notorious record is contained in correspondence between Sir Jeffery Amherst, Commander-in-Chief of the British forces in North America, and Colonel Henry Bouquet in 1763, at the time of the Pontiac rebellion:

AMHERST: "Could it not be contrived to send smallpox among these disaffected tribes of Indians? We must on this occasion use every strategem in our power to reduce them."

BOUQUET: "I will try to inoculate the—— with some blankets that may fall in their hands, and take care not to get the disease myself." (Heagerty, 1928.)

By 1785 smallpox had occurred among the Sioux Indians of the Great Plains and crossed the Rocky Mountains with them, and was reported in Alaska and California. Further south, Catholic missions in New Mexico had been invaded by smallpox much earlier, because of their contacts with New Spain.

Quarantine and isolation measures were strengthened, but often proved inadequate. A new element, variolation, entered the struggle against smallpox in 1721, which changed the situation among the whites but not the Indians. That year saw Boston's worst epidemic of smallpox in the 18th century. The epidemic in 1752 was less disastrous only because variolation was practised on a large scale (see Chapter 6, Table 6.2). In this latter outbreak, 1843 of Boston's 15 684 residents fled to the country; 5545 of the remainder caught smallpox, of whom 539 died; 2124 were inoculated, with 30 deaths, and 5998 persons had already had smallpox when the outbreak began. Only 174 susceptible persons who stayed in the city escaped infection (Blake, 1959). When smallpox broke out again in Boston, in 1792, practically the whole town was inoculated within a few days and only 69 deaths from naturally acquired smallpox occurred in the now much larger population.

Smallpox played a part in the Revolutionary Wars, General Washington being particularly anxious about the dangers of smallpox to the Continental army. Indeed, the long duration of the siege of Boston—from June 1775 to March 1776—is considered to have been due in large degree to the existence of smallpox in the city and Washington's fear of attacking it and exposing his army to the

disease. When the British finally left, on 17 March, Washington ordered "one thousand men who had had the smallpox" to take possession of the city. Further north, smallpox in the Northern army was so severe as to decide the course of the war in that region and thus the continued adherence of what is now Canada to the British Crown. In 1777 Washington ordered the compulsory variolation of all new recruits to his armies, an act which prompted a historian (Thursfield, 1940) to write "... I think it is fair to claim that an intelligent and properly controlled application of the only method then known of defeating the ravages of smallpox, which in the years 1775–76 threatened to ruin the American cause, was a factor of considerable importance in the eventual outcome of the War of Independence".

A few years later Jenner published his discovery of vaccination. This was taken up soon after by Dr Benjamin Waterhouse, the first Professor of Medicine at Harvard University, who received news of Jenner's discovery in 1799 and was immediately excited by it. Despite imperfect vaccine, widespread vaccination of the white population reduced smallpox during the early 19th century, although epidemics still occurred in the cities; between 1800 and 1850 Philadelphia had 8 epidemics, Boston 6 and Baltimore 3. Complacency and a failure to maintain supplies of the virus, as well as lack of recognition of the need for revaccination, contributed to the continued presence of smallpox among the white population, but their suffering paled before that of the Indians. Massive and devastating pandemics which occurred in 1801 1802 and in 1836–1840 led to the virtual extinction of many tribes of indigenous North Americans. The second outbreak affected the Indian population over the whole of the North American continent west of the Mississippi river, from Texas to Alaska and from St Louis to California.

One result of these terrible epidemics was the Federal decision to vaccinate the survivors, so that by the second half of the 19th century the Indians were better vaccinated than the white and black inhabitants of North America, many of whom refused vaccination. In the late 19th century smallpox was more severe in the non-Indian population, among whom there were 3 widespread epidemics, in 1865–1866, 1871–1875, and 1881–1883.

In spite of the adoption of vaccination by the United States army in 1812, this precaution was neglected when regiments were raised for the Civil War in the 1860s. In the Union army, there were 6716 cases of smallpox with 2341 deaths among the Negro troops and 12 236 cases with 4717 deaths among the 431 237 white troops. The disease spread among the Confederate army, as well as among civilians on both sides. Indeed, President Lincoln was probably febrile with the prodrome of smallpox when he gave the Gettysburg address on 19 November 1863; his rash appeared on 21 November.

The slave trade, with its threat of smallpox importations, had been made illegal in the British West Indies in 1807 and in the USA in 1808, but after the Civil War migration from Europe increased greatly, and with it the risk of further importations of smallpox from that continent. Between 1871 and 1873 there were widespread outbreaks in Philadelphia, Baltimore, Washington, Cincinnati, New York, Boston and Chicago. A smaller series of outbreaks occurred in the early 1880s, by which time the railway network helped to spread the disease rapidly throughout the continent.

The closing years of the 19th century were marked by the appearance and spread of variola minor in Canada and the USA, a phenomenon described later in this chapter and in Chapter 8 (see Chapter 8, Fig. 8.4).

SMALLPOX IN OCEANIA BETWEEN 1789 AND 1900

Oceania is a term used to embrace Australia and the islands of the Western Pacific, including New Zealand and Papua New Guinea.

Australia

The existence of a "Great South Land", to "balance" the continents of the Northern Hemisphere, had long been suspected, and from the mid-16th century onwards several European explorers had made contact with parts of it. The prelude to European colonization was the first voyage of James Cook in 1768–1771, in which he charted the east coast of Australia. The loss of its American colonies shortly after this led Great Britain to seek some other distant place for the disposal of the victims of its repressive laws, and the new continent looked ideal. The First Fleet, comprising 11 ships carrying about 1500

persons—convicts and their guards and keepers—sailed from England on 6 January 1787, called at Rio de Janeiro on 4 August and at Cape Town on 13 October, and arrived in Botany Bay, just south of the present city of Sydney, on 20 January 1788. No addition was made to the infant colony until the arrival of the Second Fleet in 1790.

The early navigators had already reported that the country was inhabited by primitive dark-skinned people, and recent archaeological studies show that aborigines had been in Australia for at least 40 000 years. The late 18th century was a period of severe smallpox in Great Britain, mitigated somewhat by the increasing adoption of variolation. Knowing that the natives of other distant lands, such as South Africa and the East Indies, were infected with smallpox, the surgeons of the First Fleet brought with them "variolous matter in bottles" for inoculation if it proved to be necessary. In fact they found a sparse population of hunter-gatherers who, like the aboriginal Americans, were free of smallpox, measles and most other of the common infectious diseases of Europeans.

However, in 1789, only a year after the landing, an outbreak of what was probably smallpox was recognized among the aborigines near the new European settlement, Sydney town, and appears to have spread far and wide among the aboriginal population of south-eastern Australia, as determined by explorers and by later commentators (Cumpston, 1914; Butlin, 1983, 1985; Campbell, 1983, 1985). None of the white settlers was affected, but one coloured seaman suffered from the disease. The origin of this outbreak has never been determined, but two possibilities have been canvassed. Although there is no record of the variolous matter brought by the surgeons of the First Fleet ever having been used, lost or stolen, it was a potential source of infection. On the other hand, the newly arrived Europeans may, by chance, have witnessed the passage through the Sydney area of a very rare epidemic of smallpox that had been introduced along the north coast of the continent and spread southwards.

There was little contact between aborigines and whites, except near Sydney, for many years after this, and smallpox appears to have been absent until 1829–1831, when it spread extensively through the indigenous population of south-eastern Australia, affecting a few Europeans as well. Once again, its origin was never determined. Two other outbreaks of smallpox occurred among the aborigines in the 1860s, the first extending from the north coast across central Australia to the southern coast between about 1861 and 1866, and the second extending along the north-west coast in 1865 1869 (Fenner, 1985). Both probably originated from the voyages of trepang traders coming from the islands to the north of Australia. Butlin (1983) has recently analysed the demographic effects of the 1789 and 1829 outbreaks and suggests that they played an important role in the great decline of the aboriginal population of south-eastern Australia in the first half of the 19th century.

The subsequent history of smallpox in Australia has been documented in great detail by Cumpston (1914). The first outbreak among Europeans occurred in Melbourne in 1857, originating from a ship hailing from Liverpool, England. There were 4 deaths among the 16 persons affected. Six other outbreaks of smallpox occurred in 3 of the colonies before the end of the 19th century, due to importations by passengers on ships; in addition, there were another 16 episodes in which one or two cases occurred, but their source could not be traced. The largest outbreak during the 19th century took place in 1881–1882 in New South Wales, with 154 recognized cases, occurring over a period of 6 months.

But for strict quarantine regulations there would have been many more outbreaks; Cumpston (1914) lists 145 ships quarantined for smallpox in Australian ports between 1828 and 1900, in which smallpox occurred but did not spread to persons on land. The passengers and crew on these vessels had acquired smallpox in many different ports; Cumpston lists 19 countries, located in every continent, as the sources of smallpox.

New Zealand

New Zealand was settled by Polynesian seafarers about a thousand years ago and by Europeans in 1840. During that year an immigrant ship arrived with cases of smallpox on board, but quarantine prevented spread to the colonists. No further mention of smallpox occurred until 1872, when 2 ships arrived with smallpox on board and 6 local cases occurred in Auckland. Between then and 1904 several other ships arrived with cases on board, but extension to the colonial popula-

tion occurred only in 1874 and 1903–1904 (Maclean, 1964).

Papua New Guinea

Smallpox was never endemic in Papua New Guinea, but occasional outbreaks occurred before and shortly after European settlement. Miklouchо-Maclay (1975), the first white man to live in the Astrolabe Bay area, noted pockmarked natives in 1872, and records that "the illness came from the north-west and many died of it".

The German colonists of northern New Guinea (Kaiser Wilhelmsland) recorded outbreaks in June 1893, introduced by a Malay seaman on a German ship, and again in 1895. They obtained vaccine from Batavia and treated "thousands of natives", but reconnaissance a year later showed that they did not entirely prevent the disease:

> "The great villages, whose armed men had previously by a show of arms prevented us from entering, now contained only the wretched remnants of their former population. The survivors greeted us with lamentations and showed us the mass graves of those claimed by the epidemic. Thanks to the vaccination program which had been carried out, it did not spread any further northward along the coast. Nor did it advance to any extent inland, as the profound hostility between the coastal and mountain inhabitants cut both parties off from all contact." (Sack & Clark, 1980.)

Other Pacific Islands

Although measles was brought to Fiji in 1875 and killed about 25% of the indigenous population, smallpox never occurred there, which was surprising in view of the large introductions of labourers and their families from India. Nevertheless, it was the fear of the introduction of smallpox that led in the 1880s to the training of young Fijians as vaccinators, and ultimately to the establishment of the Fiji Medical School.

None of the smaller Pacific islands had a population large enough to support endemic smallpox. However, smallpox is said to have reached the Palau Islands in 1783, and in 1854 an epidemic occurred in the Carolines in which 2000 of the 5000 inhabitants died. A severe epidemic in Guam in 1856 killed some 5000 persons out of the total population of 15 000 (Mumford & Mohr, 1943). In 1853 a ship from San Francisco brought smallpox to Hawaii for the first time, and the disease killed 8% of the indigenous inhabitants within 8 months. Smallpox was introduced into Easter Island in 1863–1864, when islanders who had been forcibly removed to Peru were returned to their home, following intense international pressure. The combined effects of smallpox and tuberculosis reduced the population of the island to an all-time low of 110 persons.

THE APPEARANCE AND SPREAD OF VARIOLA MINOR

As mentioned in Chapter 1, the occurrence of a distinctive very mild variety of smallpox was reported by Korté (1904) in South Africa as a disease that had been common there for some years, and it was recognized at about the same time (1896) in the USA (Chapin, 1913). The disease that Korté described as "amaas or kaffir-pox" is clearly identifiable as variola minor. Since it appeared to have been endemic in southern Africa for a few years before it was first described there (Brown, 1896), Chapin & Smith (1932) suggested that the disease first observed in Florida in 1896 may have originated in southern Africa. However, recent investigations of the biological characteristics of the viruses that caused variola minor in Brazil in the 1960s and in Botswana, Ethiopia and Somalia in the 1970s (see Chapter 2) suggest that there may have been at least two separate origins of variola minor viruses—one in North America and one or possibly two in Africa.

The descriptions of variola minor in South Africa are unequivocal (Brown, 1896; Korté, 1904), but it is difficult to visualize how the virus spread from there to countries in eastern and central Africa. Burton (1860) provides a clue to a possible independent origin of variola minor in eastern Africa. In his description of the lake regions of central Africa, he refers to smallpox as "the most dangerous epidemic" in eastern Africa, but goes on to state: "There is a milder form of the malady, called *Shúrúá*, resembling the chickenpox of Europe."

From the time of recognition of this disease entity at the end of the 19th century, southern and eastern Africa, the USA and to a lesser extent Europe appear to have been the centres of distribution of variola minor viruses. The appearance and behaviour of variola minor in different countries will be traced in greater

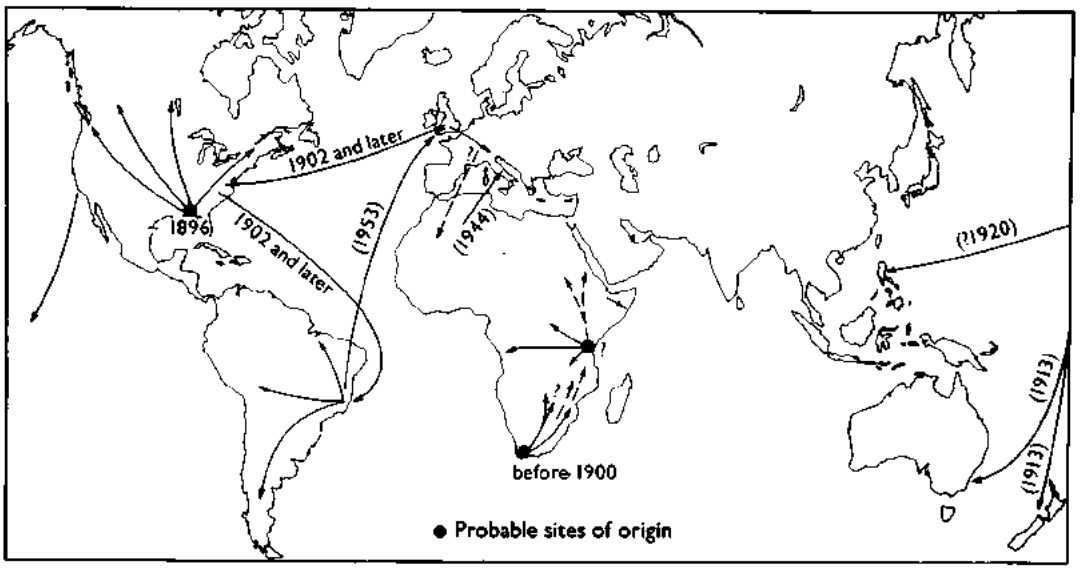


Fig. 5.8. The spread of variola minor from the USA to other parts of the world, and within Africa. Figures in brackets indicate dates of importations that did not result in the establishment of endemic variola minor.

The situation in Africa is complex and the routes of spread are unknown. Variola minor was present in South Africa from the end of the 19th century. It occurred, often together with variola major, in most countries in southern, eastern and central Africa at least from the 1930s onwards. It was probably carried from Europe across the Mediterranean to North Africa (and back to Italy in 1944) and possibly from Great Britain to the British colonies in eastern Africa. There may also have been a third, independent, focus of origin of variola minor somewhere in eastern Africa.

detail in Chapter 8, in which the smallpox situation in selected countries during the first half of the 20th century is described, but although this account covers the period beyond 1900 it is useful to give an overview of the global spread of variola minor here.

In the USA, variola minor rapidly spread all over the country (see Chapter 8, Fig. 8.4), and from there to Canada, Great Britain and South America. Later it was exported from the USA to Australia, New Zealand and the Philippines (Fig. 5.8), although it did not persist in those countries. It was the only form of endemic smallpox in Great Britain between 1920 and 1934, in the USA after 1926, and in Brazil after 1930, and was eventually eliminated from Great Britain in 1934, from the USA in the early 1940s, and from Brazil in 1971.

The spread of variola minor in Africa is much more difficult to trace, because of the lack of reliable records in most countries of that continent. It probably spread from Europe to North Africa in the 1930s, to become endemic in Algeria during the 1940s, whence it spread back to Sicily and Italy in 1944. From the 1930s variola minor occurred contemporaneously with variola major in Kenya, the Sudan, Tanganyika and Zaire. It was endemic in South Africa and neighbouring countries (present-day Botswana, Lesotho and Swaziland) from early in the 20th century, at first contemporaneously with endemic variola major; then, when this disease was eliminated (see Chapter 20), it became the only endemic form of smallpox, although there were periodic outbreaks of variola major associated with importations from other parts of Africa and from Asia.

Both varieties of smallpox occurred in the Sudan in the 1930s. Early records, reviewed by Pankhurst (1965), show that at least until the 1920s smallpox was a severe disease in Ethiopia, periodically causing outbreaks associated with high case-fatality rates. Variola minor was the only variety of smallpox found there in 1971, when the Intensified Smallpox Eradication Programme commenced operations, but there is no information about when it appeared and variola major disappeared.

SUMMARY: SMALLPOX FROM ANTIQUITY TO THE END OF THE 19th CENTURY

The origins of smallpox are unknown and most early references to it are unreliable. The

earliest credible evidence is to be found in the Egyptian mummies of persons who died some 3000 years ago. It is not unreasonable to suggest that it was transferred from Egypt by land or water to India, where it remained as an endemic human disease for some 2000 years and perhaps longer. In the 1st century AD it was introduced into China from the south-west and became established in the local population, and in the 6th century it was carried from China to Japan. In the west, smallpox made periodic incursions into Europe but did not become established there until the population increased and population movement became more active during the time of the Crusades.

As populations grew in India, China and Europe, smallpox became established in the cities and more populous areas as an endemic disease affecting mainly children, with periodic epidemics that killed up to 30% of those infected. Its impact steadily increased, and by the 16th century it was an important cause of morbidity and mortality in Europe, south-western Asia, India and China. The occurrence of the disease in Europe was of special importance, for this served as the focus from which smallpox spread to other parts of the world, as an accompaniment of successive waves of European exploration and colonization.

In 1507 smallpox was introduced into the Caribbean island of Hispaniola and in 1520 into the mainland of the Americas, in Mexico. It struck the native Amerindians with great severity and was an important factor in the conquest of the Aztecs and the Incas by the Spaniards. Settlement of the east coast of North America occurred about a century later and was also accompanied by devastating outbreaks of smallpox among the Amerindians, and subsequently among the native-born colonists.

By the mid-18th century smallpox was a major endemic disease everywhere in the world except in Australia and in several small islands. It was introduced into Australia in 1789 and again in 1829 and caused devastation among the aborigines, but quickly died out on both occasions.

The widespread use of variolation in a few countries, notably Great Britain and its North American colonies, somewhat mitigated the impact of smallpox among the wealthy classes during the latter part of the 18th century, but a real reduction in its incidence did not occur until vaccination was widely used during the 19th century. Improved vaccines and the practice of revaccination led to a substantial lessening of the ravages of smallpox in Europe and North America, but at the end of the 19th century it remained almost unchecked elsewhere.

Just before the close of the 19th century a much milder form of smallpox, variola minor, was recognized in the State of Florida, USA, and in South Africa. From Florida it spread all over the USA and then into Canada, the South American countries and Great Britain. By the mid-20th century variola minor occurred along with variola major, in varying proportions, in many parts of Africa.

CHAPTER 6

EARLY EFFORTS AT CONTROL: VARIOLATION, VACCINATION, AND ISOLATION AND QUARANTINE

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INTRODUCTION

Besides killing many of those who were infected, an attack of smallpox left most of its survivors pockmarked, and it was realized in ancient times that pockmarked persons never caught smallpox again. By accident, it was found that persons who were infected with smallpox via a scratch on the skin suffered a much less severe form of the disease.

Long ago, in places in which smallpox had become endemic, a connection must have been made between these observations, and attempts to ameliorate the severity of smallpox were initiated by administering the pustular fluid or the dried scabs to persons who had not had smallpox. The disease which followed such artificial infection was like smallpox, but usually much milder. In some such way, the practice arose of inoculation with smallpox pus or scabs—or "variolation" as it was eventually called, to distinguish it from vaccination. It may have developed independently in China and India, because different routes of inoculation, nasal and cutaneous respectively, were used in these countries. It was said to have been introduced into Egypt by the Mamelukes in the 13th century, and was known in North and western Africa, at least from the late 17th century. It is impossible to know whether it was indigenous in Africa or spread to that

Clinical Differences between Smallpox after Variolation by the Cutaneous Route and "Natural" Smallpox

Variolation would never have been adopted so widely if it had not caused a less severe disease, and been less likely to kill or cause permanent pockmarks, than naturally acquired smallpox. The difference in mortality varied, but commonly the case-fatality rate was 0.5–2% after variolation, compared with 20–30% after natural smallpox. The symptomatology was also different. A primary lesion appeared at the inoculation site on about the 3rd day (see Chapter 3, Fig. 3.1) and commonly there were satellite pustules around the site of inoculation (see Plate 6.2), but usually a much less severe generalized rash occurred than in ordinary-type smallpox. The reasons for the difference in severity are not known; possible explanations are given in Chapter 3. In any event the virus was not attenuated and one of the major disadvantages of variolation was that it could spread to susceptible contacts to produce severe natural smallpox.

continent along with smallpox itself, possibly with Arab traders who had themselves learned of the practice in India.

Early in the 18th century, variolation spread through the Balkans into central Europe and from Turkey to Great Britain and subsequently to other countries of Europe. It became popular and widely used in some countries, especially in Great Britain and its colonies in America. Then, at the end of the 18th century, Edward Jenner showed by experiment that inoculation with cowpox virus would protect people against smallpox, with very much less constitutional disturbance and danger, to themselves and others, than was the case with variolation. The new procedure rapidly became popular and was adopted all over the world, although in some countries variolation continued to be practised as well for many years.

This chapter traces the discovery, spread and popularization of variolation and subsequently of vaccination, and then outlines the way in which, in parallel with preventive inoculation, concepts of contagion led to the notions of isolation and quarantine. Table 6.1 presents a summary of the important historical events in these fields, from the 10th to the 19th century. Development of the vaccine during the first half of the 20th century is described in Chapter 7 and its use to eliminate smallpox from most of the industrialized countries during that period is outlined in Chapter 8. Chapter 11 describes later developments in vaccine production and vaccination procedures that occurred during the Intensified Smallpox Eradication Programme.

VARIOLATION

Called smallpox inoculation, insertion, engrafting, or transplantation by 18th century authors—terms derived from the horticultural procedures for inserting a bud into a plant—the practice of cutaneous inoculation of material from smallpox pustules later came to be called "variolation", to distinguish it from the practice of vaccination with material from cowpox lesions, introduced in 1798 by Edward Jenner (Plate 6.4).

Variolation and Vaccination Performed with Different Viruses

It is important to emphasize that different species of *Orthopoxvirus* were used for variolation and for vaccination. The active agent in variolation was variola virus, the agent that caused smallpox in man, and after a successful cutaneous inoculation there was always a severe local lesion, usually with many satellite pustules (Plates 6.1–6.3), and a generalized rash customarily occurred that was sometimes quite extensive. Severe constitutional symptoms were common and sometimes subjects died of smallpox produced by variolation. Inoculation of variola virus by insufflation (the Chinese method), if successful, also produced a generalized rash and usually more severe symptoms than those produced by cutaneous variolation. Unlike the viruses later used for most other live virus vaccines, the agents used for vaccination

Table 6.1. Important events in the history of smallpox control, from ancient times to 1900

Variolation	Vaccination	Isolation and quarantine
10th century		
Variolation first reported in China, by insufflation, as a secret rite. Probably also practised in India at this time, by cutaneous inoculation.		Hospitals for smallpox established in Japan (*Ishinho*, 982).
13th century		
Variolation by cutaneous route introduced into Egypt by Mamelukes.		
17th century		
Variolation more widely used in China. K'ang Hsi (1661–1722) variolated his soldiers and his children.		Quarantine introduced to control entry of smallpox into North American ports (Boston, New York, Philadelphia; 1650s). Mandatory isolation of smallpox cases at home (Virginia, 1667).
18th century		
Papers on variolation published by Royal Society of London (Chinese method, 1700; Turkish method: Timoni, 1714; Pylarini, 1716). Cotton Mather told of variolation by his African slaves (Boston, 1706). Variolation by cutaneous route carried out in Great Britain (Sloane, 1721), Bohemia (Reiman, 1721) and Boston, USA (Boylston, 1721). Variolation popularized in England by the Suttons (1726). Dimsdale variolates Catherine the Great and variolation accepted in Russia (1768). Louis XV dies of smallpox and variolation accepted in France (1774). Washington orders variolation of the Continental army (1777).	Publication of Jenner's *Inquiry* (1798).	London Small-Pox and Inoculation Hospital established (1746). Eradication of smallpox by systematic variolation of population and isolation of cases suggested by Haygarth (1793) and Carl (1799).
19th century		
Variolation banned in Russia (1805), Prussia (1835), Great Britain (1840) and British India (1870), but still widely practised in Afghanistan, China and many parts of Africa.	*Inquiry* translated into several European languages (1800–1802). Vaccination adopted in most European countries and in the USA (1800–1803). Vaccine sent successfully to Bombay (de Carro, 1802) and to South and Central America, the Philippines and Macao (Balmis-Salvany Expedition, 1803–1806). Primary vaccination of infants made compulsory in Bavaria (1807), Denmark (1810), Norway (1811), Bohemia and Russia (1812), Sweden (1816), Hanover (1821) and Great Britain (1853). Revaccination introduced into Württemberg (1829). Vaccination compulsory in Prussian army (1833). Vaccine produced in calves (Italy, 1805, 1810). Vaccine passaged in calves for production (Negri, 1840). Production in calves adopted in France (1864), Belgium (1865), Great Britain (1881) and Germany (1884). Use of glycerol as diluent introduced in Italy (Negri, 1840s). Glycerolated vaccine popularized by Copeman (1892). Jenner's arm-to-arm vaccination banned in Great Britain (1898).	Control of smallpox by isolation of cases and quarantine of contacts ("Leicester method", 1870); reinforced by vaccination of contacts (Millard, 1914).

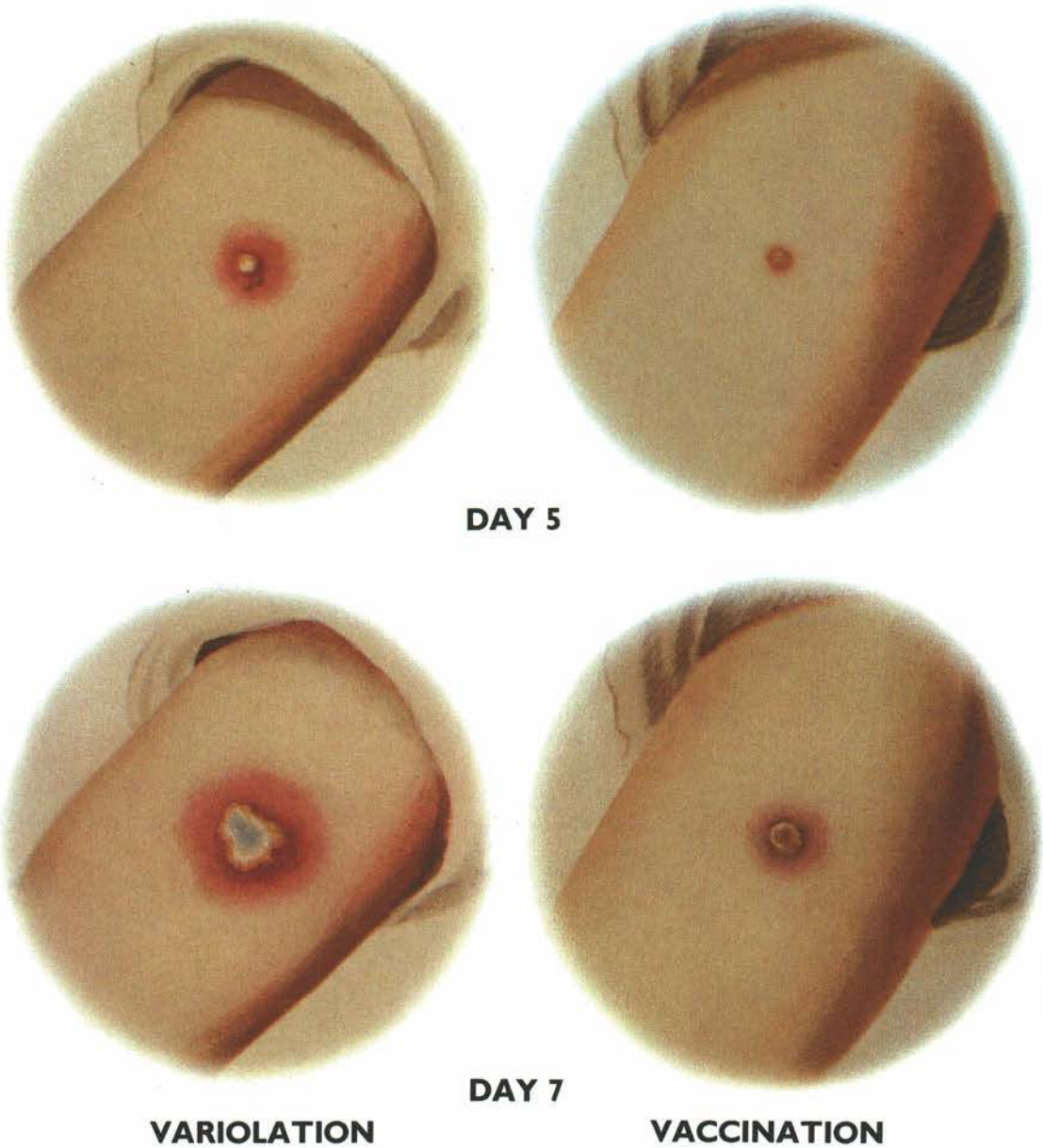

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Plate 6.1. Engravings by George Kirtland of coloured drawings made in 1801 by Captain C. Gold, showing the appearance of the local lesions at various times after variolation and vaccination. They were published by Kirtland in 1806 and independently reproduced from the original drawings in the Jenner Centenary Number of the *British medical journal*, published on 23 May 1896. Variolation and vaccination are represented on the 5th and 7th days after inoculation.

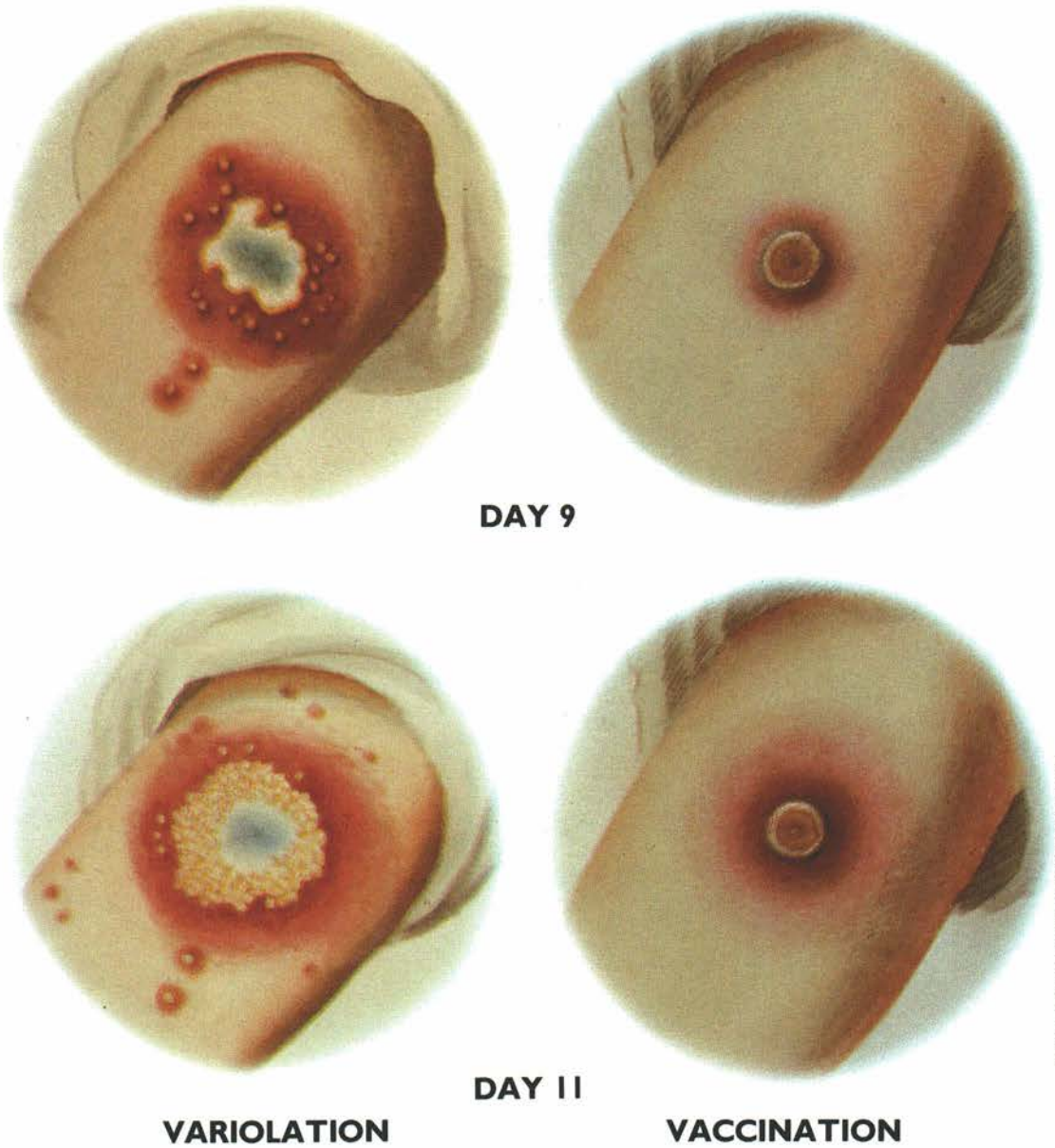

Plate 6.2. The Gold-Kirtland drawings. Variolation and vaccination on the 9th and 11th days after inoculation.

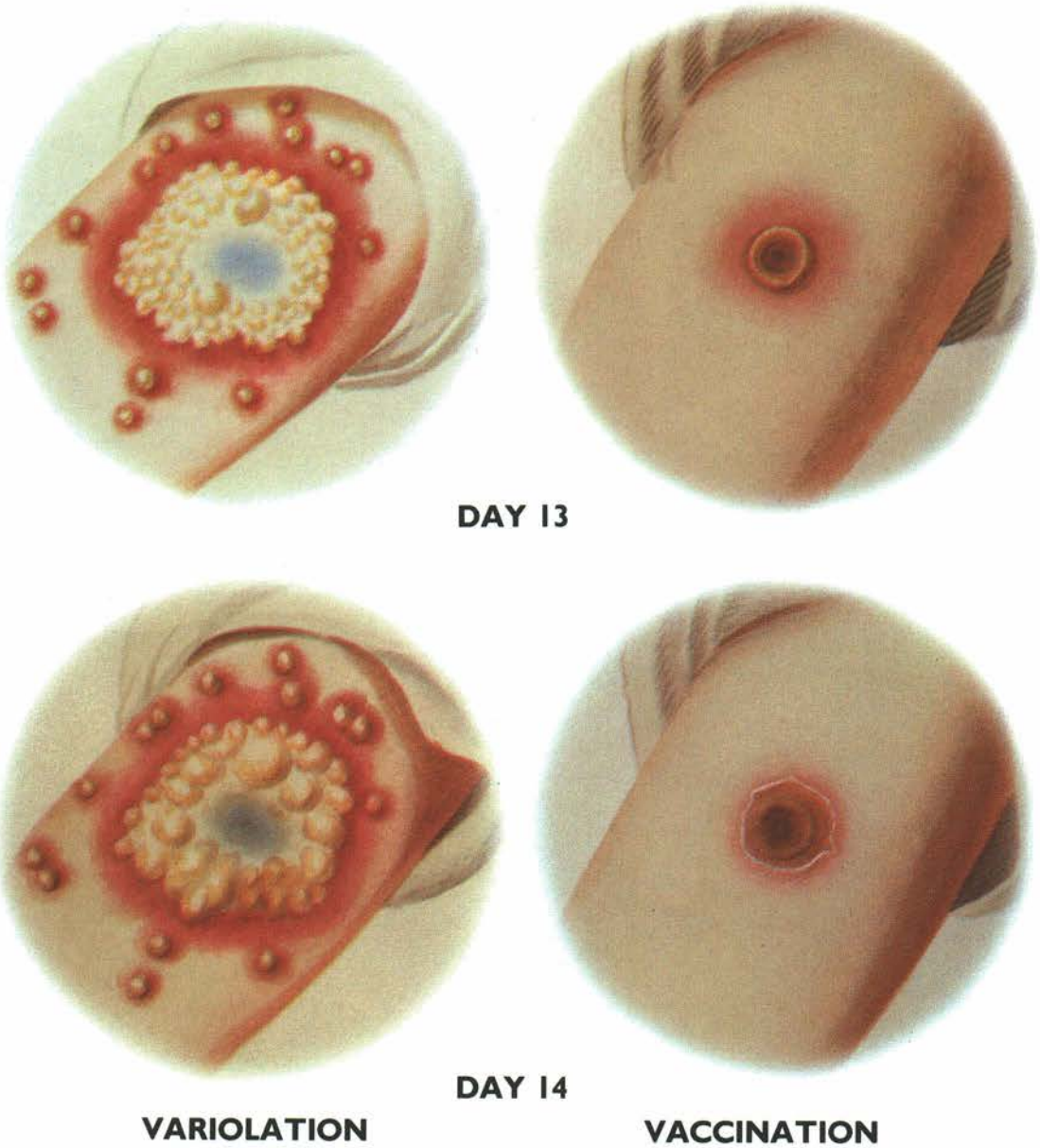

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Plate 6.3. The Gold-Kirtland drawings. Variolation and vaccination on the 13th and 14th days after inoculation.

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Plate 6.4. Edward Jenner. (1749-1823). Pastel portrait by J. R. Smith in 1800.

The Art of Variolation in China

"... the art was first taught by a nun in the reign of Jen Tsung (A.D. 1023–63). That reign was signalised by a famous premier, Wang Tan, a great statesman and scholar. Small-pox had deprived him of all his children, and when in old age a son was born to him he was most solicitous to secure for that child a safe attack of the fell disorder ... An officer at the capital, a native of Szechwan, hearing of the circumstances, obtained an introduction to the minister and gave him the following information. A young woman of Kiangsu vowed to quit the world, and, rejecting marriage, devoted herself to the worship of Buddha, but refused submission to the tonsure, preferring to retain her hair. She wandered to Omei Mountain (sacred to Sakyamuni, contiguous to Thibet), and on its summit lived in a reed hut. The women of all that region became her disciples, fasting, reciting prayers and doing good. Recently she told her followers that she had been inspired to impart instruction in implanting smallpox, which consisted in selecting scabs from cases that had had but few pustules, and these pointed, round, red and glossy, full of greenish-yellow pus that became thick. The scabs to be used when a month old, or in hot weather those that had fallen only 15 or 20 days might be used, while winter ones should be 40 or 50 days old before using, which may be in spring or autumn. Take 8 grains of the desiccated scabs and 2 grains of *Uvularia grandiflora*; pound the two together in a clean earthen mortar. Select lucky and eschew unlucky days for implanting. Employ for the operation a silver tube curved at the point; blow the prepared matter into the right nostril in the case of a boy, and into the left in girls; six days after there is slight fever, which on the following day increases greatly; in two or three days more an eruption appears, charged with matter, and then scabs. Not one in 10, not one in 100, that does not recover. All the inhabitants of the region adjacent to Omei Mountain adopted the practice, praying her to perform the operation. On hearing this the minister sent for the venerable recluse, who came to the capital and operated successfully ... She returned to the sacred mountain, and some years later informed her followers that she was not uterine born, but was an incarnation of the Goddess of Mercy, and had come to preserve the lives of children by implanting small-pox, 'which,' said she, 'I have taught you, that you should impart the art to others.' On hearing this announcement the women all worshipped her, lauding her righteousness, asking by what title they should invoke her. She answered, 'As Your Ladyship the Celestial Mother,' adding 'whenever anyone shall offer incense and prayers to me, invoking my intervention, I will from heaven manifest myself by turning malignant into benignant cases'; whereon she was transformed, that is, she died. Every official temple has a shrine to this 'Goddess of Smallpox' and many cities have temples for her exclusive worship. Evidently inoculation had been taught at Omei Mountain by some Thibetan monk, who had acquired his art in India, where it appears to have been known in high antiquity." (Macgowan, 1884.)

against smallpox were not attenuated strains of the virus that caused smallpox (variola virus), but a totally different species of *Orthopoxvirus*, initially cowpox virus and subsequently vaccinia virus. Both these viruses produced a localized lesion at the site of cutaneous inoculation, without satellite or generalized lesions except in very rare cases, and they were only very rarely transmissible to other persons. Neither cowpox nor vaccinia virus can be "transformed" into variola virus, nor is the reverse possible (see Chapter 2); both provided a high degree of protection against smallpox, for at least several years.

Variolation in China

The early practice of variolation is better documented in Chinese literature (Needham, 1980) than in Indian. It appears to have begun as a secret procedure about AD 1000, and did not become public knowledge until about AD 1500, when writings about it appeared in Chinese medical books. The mode of inoculation was by the intranasal insufflation of powdered scab material (see Plate 6.14B). Descriptions of the method of preparing the inoculum show a realization that its activity persisted for longer in winter than in summer

Method of Variolation in India

"The operation of inoculation called by the natives *tikah* has been known in the kingdom of Bengall as near as I can learn, about 150 years . . . Their method of performing this operation is by taking a little pus (when the small-pox are come to maturity and are of a good kind) and dipping these in the point of a pretty large sharp needle. Therewith [they] make severall punctures in the hollow under the deltoid muscle and sometimes in the forehead, after which they cover the part with a little paste made of boiled rice." (Coult, 1731.)

and that it was sensitive to sunlight and excessive heat. Fresh scab material was supposed to be stored "on the person" (i.e., at about 37 °C) for up to a month, a prescription that ensured that it contained little active virus, but consisted in large part of inactivated virus. Intranasal insufflation was still employed as a method of variolation in some parts of China in the 20th century (Tao, 1935). Cutaneous inoculation with variola virus appears not to have been practised there until after vaccination by the same route had been introduced in 1805 (Jiang Yutu, personal communication, 1982). Surprisingly, the Japanese were ignorant of variolation until about the mid-18th century, when the practice was introduced from China.

Variolation in India and South-western Asia

Hopkins (1983a) suggests that variolation had been practised in India for centuries, an opinion with which we agree, although there is no documented evidence of its use before Europeans settled there in the 16th century. From then onwards there are several references to inoculation against smallpox, usually by the cutaneous route, in the writings of European visitors. Variolation was made illegal in British India in 1870, but it continued to be practised on a reduced scale, particularly in the princely states, until recent times. It was common in Afghanistan and parts of Pakistan up to the 1970s, occasionally accompanied by a high case-fatality rate (see Chapter 14).

From India the practice spread to various countries in south-western Asia and thence into central Europe via the Balkans, and probably with Arab slave traders to eastern and western Africa. However, nowhere in Asia was variolation used as a systematic large-scale effort to prevent smallpox, in the way it was developed by some of its practitioners in Great Britain during the latter part of the 18th century.

Detailed European knowledge of variolation came via two routes: through the Balkans to central Europe, where it was extensively practised in Slovakia very early in the 18th century (Dubay, 1972), and from the Turks in Constantinople, where it is said to have been introduced during the 17th century, probably from India. The Ottoman Empire was then a powerful independent state, the nearest place to Europe in which the "exotic practices" of the Orient could be seen at close hand, and a succession of descriptions of the procedure of inoculation were made by European visitors to Turkey.

Introduction of Variolation into Europe

In contrast to the paucity of published information on variolation elsewhere, there is a large literature on its introduction and spread in Europe (Miller, 1957) and North America. Variolation was important in Europe not only because it was practised on a scale that far exceeded that attained elsewhere, and probably influenced the incidence of smallpox in some European countries (Razzell, 1977b), but also because it set the stage for Jenner's discovery of vaccination and its rapid acceptance. Of all the European countries, Great Britain was the most important, as far as variolation was concerned, and the Royal Society of London played a critical role as the focus for reports on the practice elsewhere in the world.

There were apparently folk practices in several parts of Europe in the latter part of the 17th century of "buying the smallpox", which involved sending children to homes in which a patient was recovering from smallpox to buy

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Plate 6.5. Lady Mary Wortley Montagu (1689–1742). Suffered from smallpox in 1715 and was left severely pockmarked. Learned of variolation in Constantinople. Her daughter was the first person to be professionally inoculated in Great Britain, in 1721.

some crusts for a penny or two. Also, children were sometimes deliberately exposed to mild cases, or "bedded" with other children who had mild smallpox, so that they might get the disease in favourable circumstances (Miller, 1957).

But, as Samuel Johnson remarked, during the 18th century there was a great passion for innovation, and for innovation from lands foreign to European traditions and knowledge. Thus in the year 1700 two independent reports were made to the Royal Society of London describing the Chinese method of variolation by intranasal insufflation. Then in 1714 and 1716 accounts of the Turkish method of cutaneous inoculation were independently communicated to the Royal Society by the physicians Emanuele Timoni and Jacob Pylarini. However, British doctors were too conservative to follow up these suggestions immediately, in spite of the severity of smallpox at that time.

Lady Mary Wortley Montagu (Plate 6.5) is widely credited with having introduced variolation into Great Britain in 1721, as the funeral monument erected in 1789 in Lichfield Cathedral, 27 years after her death in 1762, attests:

"Sacred to the memory of the right honourable Lady Mary Wortley Montagu, who happily introduced, from Turkey, into this country, the salutary art of inoculating the small pox. Convinced of its efficacy, she first tried it with success on her own children, and then recommended the practice of it to her fellow-citizens. Thus, by her advice, we have softened the virulence, and escaped the danger of this malignant disease."

Miller (1981) suggests that this is too simple an explanation, and argues that the introduction of variolation into Western medicine is a classic example of how innovation in medical practice occurs. The process includes the urgent need for a method of prevention or cure, a promising solution, a strongly supported programme of experimentation and study and prominent examples of the effectiveness of the new procedure if it is to gain acceptance. With inoculation against smallpox, the first component was obvious and the second provided by the succession of reports and discussions at the Royal Society of London on inoculation as practised in China and Turkey. The major force in study and experimentation was Sir Hans Sloane, who was the king's physician and President of the Royal Society. Through his influence, when the time was ripe, royal sanction was given to experiments on prisoners, and then prominent examples of its use were provided when in April 1722 two royal princesses, Amelia and Caroline, were inoculated, under Sloane's supervision. By the end of the century, Woodville (1796), in his comprehensive history of variolation, extolled Lady Mary's virtues and concluded: "It is therefore highly probable, had it not been for the uncommon fortitude of Lady Mary Wortley Montague ... that the era of the commencement of inoculation in this country would have been much later than here stated." Miller attributes the credit given to Lady Mary Wortley Montagu to her vivacity and prominence in British society, her considerable skill with the pen, the common knowledge that her daughter was the first person in Great Britain to be inoculated, and the advertisement of her activities, especially by Voltaire.

In the same year as this highly publicized operation, Dr Johann Adam Reiman carried out smallpox inoculations in Bohemia, following earlier articles (see, for example, Reiman, 1721) discussing the rationale of the practice. The 250th anniversary of Reiman's performance of the first variolation in continental Europe was celebrated by a scientific

conference in Prešov, Czechoslovakia, in 1972 (Dubay, 1972). Clearly, smallpox was then so severe in Europe, and contacts with the East were sufficiently numerous, that the time was ripe for the introduction of the only palliative measure known.

The practice spread in Great Britain, although not without opposition, which was based partly on theological grounds and partly on its association with some mortality and with the spread of smallpox to uninoculated contacts. But it was clear from early statistical studies by Jurin (1722) that there was much less of a risk of dying from inoculated smallpox than from naturally acquired smallpox. James Jurin, who was then Secretary of the Royal Society, requested information from inoculators about details of all their inoculations, including a complete description of any fatal cases. The response was excellent, and the Royal Society files contain numerous letters from inoculators and from laymen interested in the practice (Miller, 1981). Jurin produced a series of annual reports between 1723 and 1727 which demonstrated that variolation conferred immunity, since by 1727 there would have been ample opportunity for inoculated subjects to have acquired the natural infection. The death rate for natural smallpox remained constant, at 1 death in every 6 cases; the death rate for inoculated smallpox varied from 1 in 48 to 1 in 60 cases.

Thus, beginning in the 1720s, variolation became an acceptable medical practice in Great Britain, for a combination of reasons that did not operate at the time in other countries of Europe. Opposition was particularly strong in France (Miller, 1957), until it was overcome by the mathematician and geographer, Charles de La Condamine, who began a campaign in 1754 by suggesting that nearly a million deaths could have been averted in France if the country had followed the British precedent in 1722.

The further history of variolation in Europe, especially in France and Great Britain, is developed at length in books by Miller (1957) and Razzell (1977b). The practice having once been accepted by the medical profession of the day, the practitioners of inoculation developed elaborate and expensive regimens to "prepare" children for inoculation and treat them during the ensuing illness, and the incision for inoculation itself became much deeper than previously. Its popularity waxed and waned, depending on a variety of factors: the severity of smallpox at the time, the occurrence of cases and especially deaths among members of Europe's royal families, and encouragement from across the Atlantic. In 1746 the London Small-Pox and Inoculation Hospital was established, and together with the Foundling Hospital it offered variolation free. Further advances occurred in Great Britain in the

"Preparation" for Variolation

In contrast to the way variolation was performed in Turkey, members of the medical profession in Europe made a deep incision, and, influenced by a belief in the humoral pathology of smallpox, prescribed an elaborate procedure of preparation before carrying out the operation. This was designed to "weaken" constitutions that were too "high", a condition thought to occur in robust and active individuals and accentuated by meat-eating. Preparation therefore took the form of purging, bleeding and restriction to a light diet, which were the measures then used by the medical profession for the treatment of natural smallpox. For example, the regimen was said to include emetics, purgatives and sometimes bleeding, and an abstention from animal food and strong liquors. The period of preparation was lengthened, and for Edward Jenner, when he was variolated as a boy in 1756, the preparation lasted 6 weeks. "He was bled, to ascertain whether his blood was fine; was purged repeatedly till he became emaciated and feeble; was kept on a very low diet, small in quantity, and dosed with a diet-drink to sweeten the blood." Subsequently the procedure was simplified, but not greatly shortened until the late 1760s, when the Suttons' advocacy of a short preparation and a shallow incision popularized variolation in Great Britain. (Based on Razzell, 1977b.)

1760s, when Robert Sutton perfected a much simpler technique of inoculation and, with his six sons, practised it on a large scale. The Suttonian method was in many ways a return to the practice in Constantinople, where the British had learned of variolation: a short period of preparation, or none at all in the face of an epidemic of smallpox, a shallow incision, fresh pustule fluid and no dressing. However, Thomas Dimsdale (1781) criticized the Suttons for allowing their patients to move freely in the community, a practice which produced many cases of smallpox among uninoculated contacts.

The simplified Suttonian method commended itself to physicians elsewhere in Europe, but not before an unprecedented number of royal personages had contracted smallpox, with devastating political effects when one death followed another (Hopkins, 1983a). Other notable events included the inoculation of the Tsarina of Russia, Catherine II, in 1768, by Dimsdale and, eventually, the acceptance of variolation by the French, which was precipitated by the quite unexpected death of Louis XV from smallpox on 19 May 1774.

In Great Britain, variolation by the Suttonian method was practised on a wide scale (Razzell, 1977b), but tended to be neglected in the large towns and cities, in which the risk of dying of smallpox actually increased towards the end of the 18th century.

As well as advocating the Suttonian method, Dimsdale (1767, 1781) recommended measures to prevent spread from inoculated subjects, including "general inoculation" of all the inhabitants of a village at one time, with isolation of those not well enough to be inoculated, since "more lives are now lost in London than before inoculation commenced and the community at large sustains a greater loss". Eventually, in 1793, John Haygarth (Plate 6.6) published "a sketch of a plan to exterminate the casual small-pox from Great Britain" (Haygarth, 1785, 1793; Downie, 1965b) which included "systematic inoculation throughout the country, isolation of patients, decontamination of potentially contaminated fomites, supervised inspectors responsible for specific districts, rewards for observance of rules for isolation by poor persons, fines for transgression of those rules, inspection of vessels at ports, and prayers every Sunday" (Hopkins, 1983a). Carl (1799), then Director of the Inoculation Institute in Brno (Bohemia), made a similar proposal.

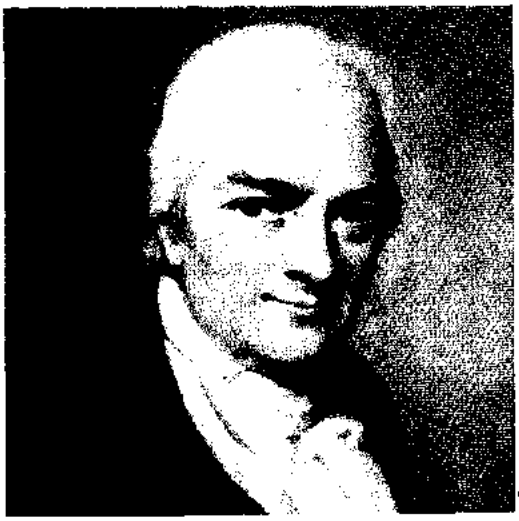

Plate 6.6. John Haygarth (1740–1827). Published excellent disease statistics for the city of Chester and developed a plan for the extermination of smallpox from Great Britain by general variolation and the isolation of cases.

The way was prepared for Edward Jenner, who had himself been inoculated as a boy and had practised variolation as a physician, to substitute cowpox virus for variola virus and thus do away with variolation—a development that would ultimately vanquish smallpox forever.

Introduction of Variolation into the Americas

Roman Catholic missionaries from Portugal introduced variolation into Brazil in 1728, but it was not much used there. Spain had been very slow to accept variolation, and it was not introduced into the colonies of New Spain until the latter part of the 18th century: Chile in 1765, Venezuela in 1769, Argentina in 1777, Peru in 1778, Mexico in 1779 and Guatemala in 1780.

The situation was very different in the British colonies in North America. Stimulated by the occurrence of a severe epidemic of smallpox in Boston in 1721, the Reverend Cotton Mather (Plate 6.7) persuaded a local physician, Dr Zabdiel Boylston, to try variolation as a method of controlling the disease (Blake, 1959). Mather had first learned of the practice from his African slaves in 1706 and had subsequently read the articles

Table 6.2. The use of variolation for the control of natural smallpox in Boston[a,b]

Year	Population	Had smallpox before	Presumed susceptible	Natural smallpox		Inoculation smallpox		Percentage of smallpox cases due to variolation	Left town	Escaped disease
				Number of cases	Case-fatality rate (%)	Number of cases	Case-fatality rate (%)			
1721	11 000	..	..	5 759	14.6	287	2.1	2	..	..
1730	13 000	..	..	3 600	13.9	400	3.0	10	..	..
1752	15 684	5 998	9 686	5 545	9.7	2 124	1.4	28	1 843	174
1764	15 700	*ca.* 8 370	*ca.* 7 330	699	17.7	4 977	0.9	87	1 537	519[c]
1776	..	..	..	304	9.5	4 988	0.6	90	..	..
1778	..	..	..	122	32.8	2 121	0.9	95	..	..
1792	19 300	*ca.* 10 300	*ca.* 9 000	232	29.8	9 152[d]	2.0	97	262	221

[a] Based on Blake (1953).
[b] .. = data not recorded.
[c] Most of these were out of town during the epidemic.
[d] Including 1038 non-residents inoculated in Boston.

by Timoni and Pylarini in the Philosophical Transactions of the Royal Society of London. Variolation at first provoked a violent controversy, but the results of its limited use in the Boston epidemic—6 deaths among 244 inoculated persons (2.5%), compared with 844 deaths among 5980 people who had contracted "natural" smallpox (14.1%)—led to its wider adoption in the colonies, especially in Philadelphia. Nevertheless, there was continued concern about the risk of inoculated persons spreading smallpox; this made the citizens of the colony receptive to Jenner's proposal to use cowpox vaccine, which did not carry this danger. However, even before the era of vaccination, Boston and other towns in Massachusetts achieved a measure of control of smallpox (Table 6.2) by combining widespread variolation under careful supervision, including inoculation of the poor, with strict policies of quarantine and isolation.

So great was the disruption of his military plans by smallpox that George Washington, after considerable hesitation, ordered the compulsory variolation of new recruits to the Continental army early in 1777.

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Plate 6.7. Reverend Cotton Mather (1663–1728). Had learned about variolation from his African slaves in 1706 and arranged for Dr Zabdiel Boylston to carry out the first variolations in North America in 1721. Portrait by Peter Pelham.

Variolation in Africa

The earliest reference to the existence of variolation in Africa was the discussion between Cotton Mather and his slaves in 1706, which indicated that cutaneous inoculation was a common practice before that time in some parts of western Africa. Later references from European travellers, traders and explorers, summarized by Herbert (1975), show that variolation was widespread in Africa throughout the 19th century. Smallpox was introduced into central Africa late in its history, probably during the early years of the 19th century (see Chapter 5); variolation appears to have been introduced soon afterwards, probably via Arab-led caravans. It was rarely practised on a scale that had an appreciable influence on the overall incidence of smallpox. In some places variolation of all those who had not yet had the disease was carried out when the first cases of smallpox occurred in a village, using material from these cases. Elsewhere—in Ethiopia, for example—the head of a house

would obtain material when there were reports of cases in the vicinity and variolate the members of his extended family.

The site of inoculation varied from place to place—for example: the forehead, the arm, the leg and the "anatomist's snuff-box" (on the dorsum of the hand at the base of the metacarpal of the thumb) in different parts of Africa; the forearm and the anatomist's snuff-box in Afghanistan and Persia. At the turn of the century the French authorities were concerned about the growing popularity of variolation (in preference to vaccination) in Algeria, and it was suggested that the practice "ought to be sternly suppressed in all French colonies" (*Lancet*, 1901). However, variolation continued to be practised up to modern times and was encountered during the eradication programmes in western, eastern and southern Africa (see Chapters 17, 19, 20 and 21).

THE DISCOVERY OF VACCINATION

The second half of the 18th century saw smallpox at its most destructive stage in Europe, and by this time the practice of variolation was well established as a preventive measure, although it was recognized that occasionally inoculated subjects died and perhaps more often they conveyed severe disease ("natural" smallpox) to their susceptible contacts. There was also the observation among country folk in several parts of Europe that milkmaids were rarely pockmarked, and the local belief was that they were protected because of an infection acquired from cows. As Jenner testified to the House of Commons in 1802, the "vague opinion" of the protective value of cowpox had arisen quite recently among farmers and was probably connected with the observation of the insusceptibility of milkmaids to variolation, practised much more widely during the late 18th century because of Sutton's improved method.

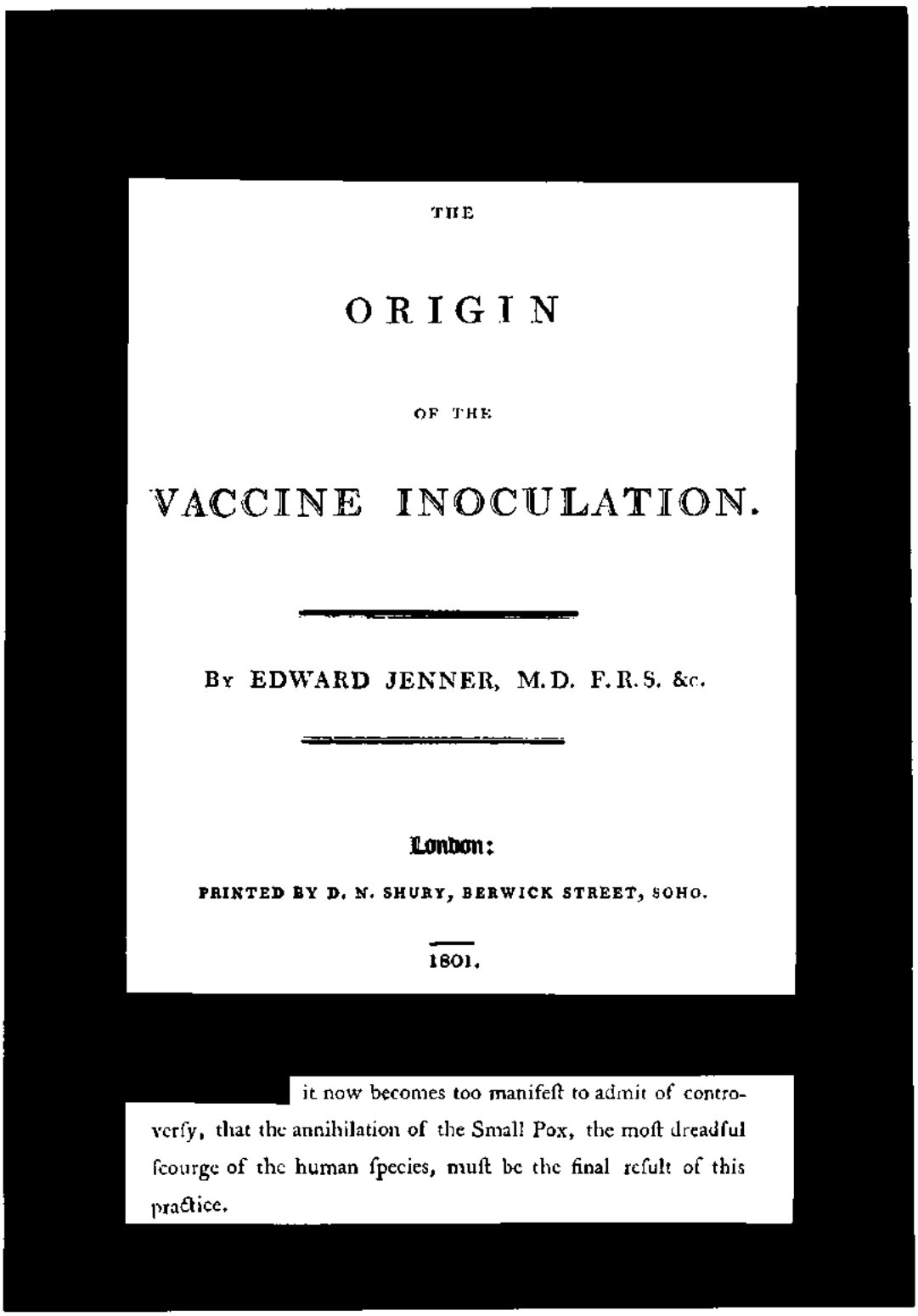
A few educated men took up this story and when they found a case of cowpox they inoculated material from it into their children. After Edward Jenner had demonstrated by challenge inoculation with variola virus that subjects inoculated previously with cowpox were indeed resistant to smallpox, claims for priority were made by several of these people: Fewster in 1765, Bose in 1769, Jesty in 1774, Nash in 1781 and Platt and Jensen in 1791 (Dixon, 1962; Baxby, 1981). However, without denying that each of these claimants may have made an inoculation with cowpox to protect against smallpox, the principal credit must go to Edward Jenner, who demonstrated its protective effect by subsequent challenge inoculation with smallpox virus, published his results (Jenner, 1798), and for the rest of his life actively promoted the cause of vaccine inoculation (Baron, 1838; LeFanu, 1951). Subsequently, to honour Jenner, Pasteur (1881) generalized the use of the term "vaccination" to include preventive inoculation with all kinds of infectious agents.

Jenner's Observations and Experiments

We cannot do better than Jenner himself in summarizing how he came to carry out the famous experiments on James Phipps on 14 May 1796 (Plate 6.8; Jenner, 1801).

"My inquiry into the nature of the Cow Pox commenced upwards of twenty-five years ago. My attention to this singular disease was first excited by observing, that among those whom in the country I was frequently called upon to inoculate, many resisted every effort to give them the Small Pox. These patients I found had undergone a disease they called the Cow Pox, contracted by milking Cows affected with a peculiar eruption on their teats. On inquiry, it appeared that it had been known among the dairies from time immemorial, and that a vague opinion prevailed that it was a preventive of the Small Pox. This opinion I found was, comparatively, new among them; for all the older farmers declared they had no such idea in their early days—a circumstance that seemed easily to be accounted for, from my knowing that the common people were very rarely inoculated for the Small Pox, till that practice was rendered general by the improved method introduced by the Suttons: so that the working people in the dairies were seldom put to the test of the preventive powers of the Cow Pox.

"In the course of the investigation of this subject, which, like all others of a complex and intricate nature, presented many difficulties, I found that some of those *who seemed to have undergone the Cow Pox*, nevertheless, on inoculation with the Small Pox, felt its influence just the same as if no disease had been communicated to them by the Cow. This occurrence led me to inquire among the medical practitioners in the country around me,



THE

ORIGIN

OF THE

VACCINE INOCULATION.

By EDWARD JENNER, M.D. F.R.S. &c.

London:

PRINTED BY D. N. SHURY, BERWICK STREET, SOHO.

1801.

it now becomes too manifeſt to admit of controverſy, that the annihilation of the Small Pox, the moſt dreadful ſcourge of the human ſpecies, muſt be the final reſult of this practice.

Plate 6.8. Jenner's forecast of smallpox eradication. The full text of this paper is reproduced in this chapter.

who all agreed in this sentiment, that the Cow Pox was not to be relied upon as a certain preventive of the Small Pox. This for a while damped, but did not extinguish, my ardour; for as I proceeded, I had the satisfaction to learn that the Cow was subject to some varieties of spontaneous eruptions upon her teats; that they were all capable of communicating sores to the hands of the milkers; and that whatever sore was derived from the animal, was called in the dairy the Cow Pox. Thus I surmounted a great obstacle, and, in consequence, was led to form a distinction between these diseases, one of which only I have denominated the *true*, the others the *spurious*, Cow Pox, as they possess no specific power over the constitution. This impediment to my progress was not long removed, before another, of far greater magnitude in its appearances, started up. There were not wanting instances to prove that, when the true Cow Pox broke out among the cattle at a dairy, a person who had milked an infected animal, and had thereby apparently gone through the disease in common with others, was liable to receive the Small Pox afterwards. This, like the former obstacle, gave a painful check to my fond and aspiring hopes: but reflecting that the operations of Nature are generally uniform, and that it was not probable the human constitution (having undergone the Cow Pox) should in some instances be perfectly shielded from the Small Pox, and in many others remain unprotected, I resumed my labours with redoubled ardour. The result was fortunate; for I now discovered that the Virus of Cow Pox was liable to undergo progressive changes, from the same causes precisely as that of Small Pox; and that when it was applied to the human skin in its degenerated state, it would produce the ulcerative effects in as great a degree as when it was not decomposed, and sometimes far greater; but having lost *its specific properties*, it was incapable of producing that change upon the human frame which is requisite to render it unsusceptible of the variolous contagion ...

"During the investigation of the casual Cow Pox, I was struck with the idea that it might be practicable to propagate the disease by inoculation, after the manner of the Small Pox, first from the Cow, and finally from one human being to another. I anxiously waited some time for an opportunity of putting this theory to the test. At length the period arrived. The first experiment was made upon a lad of the name of Phipps, in whose arm a little Vaccine Virus was inserted, taken from the hand of a young woman who had been accidentally infected by a cow [Sarah Nelmes; Plate 6.9]. Notwithstanding the resemblance which the pustule, thus excited on the boy's arm, bore to variolous inoculation, yet as the indisposition attending it was barely perceptible, I could scarcely persuade myself the patient was secure from the Small Pox. However, on his being inoculated some months afterwards, it proved that he was secure.* This case inspired me with confidence; and as soon as I could again furnish myself with Virus from the Cow, I made an arrangement for a series of inoculations. A number of children were inoculated in succession, one

"* This boy was inoculated nearly at the expiration of five years afterwards with variolous matter, but no other effect was produced beyond a local inflammation around the punctured part of the arm."

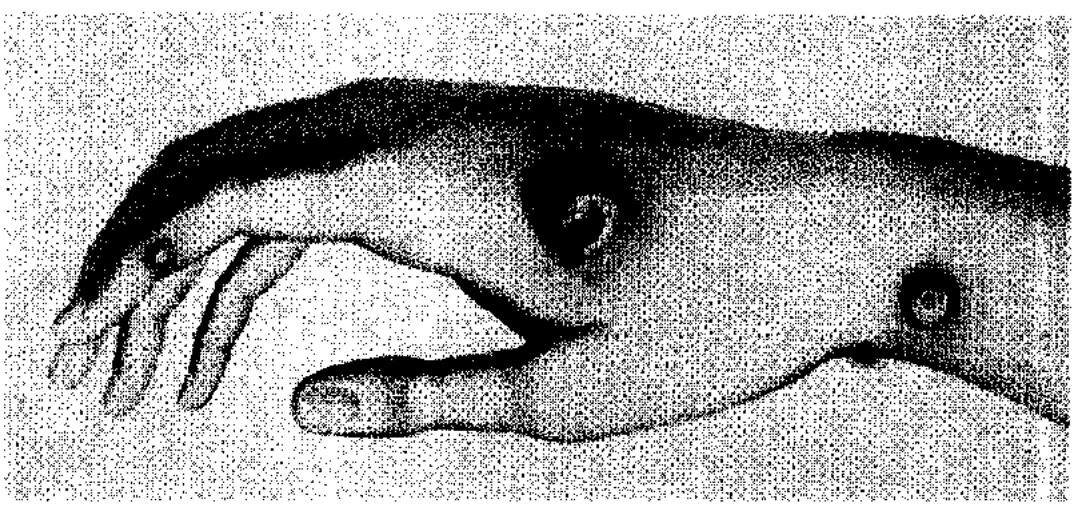


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Plate 6.9. Accidental cowpox lesions on the hand of Sarah Nelmes (case XVI in Jenner's *Inquiry*) from which material was taken for the vaccination of James Phipps in 1796.

from the other; and after several months had elapsed, they were exposed to the infection of the Small Pox; some by Inoculation, others by variolous effluvia, and some in both ways; but they all resisted it. The result of these trials gradually led me into a wider field of experiment, which I went over not only with great attention, but with painful solicitude. This became universally known through a Treatise published in June 1798. The result of my further experience was also brought forward in subsequent publications in the two succeeding years, 1799 and 1800. The distrust and scepticism which naturally arose in the minds of medical men, on my first announcing so unexpected a discovery, has now nearly disappeared. Many hundreds of them, from actual experience, have given their attestations that the inoculated Cow Pox proves a perfect security against the Small Pox; and I shall probably be within compass if I say, thousands are ready to follow their example; for the scope that this inoculation has now taken is immense. An hundred thousand persons, upon the smallest computation, have been inoculated in these realms. The numbers who have partaken of its benefits throughout Europe and others parts of the Globe are incalculable: and it now becomes too manifest to admit of controversy, that the annihilation of the Small Pox, the most dreadful scourge of the human species, must be the final result of this practice."

Jenner's home in Berkeley, Gloucestershire (Plate 6.10), has been purchased by the Jenner Trust. It has been developed as a museum which commemorates not only Jenner but also the application of his discovery to the global eradication of smallpox, achieved 181 years after his experiments on Phipps.

The World-wide Acceptance of Vaccination

At the beginning of the 19th century the educated public was receptive to Jenner's idea. Unlike many other diseases that were common at the time, smallpox struck at all levels of society and was the object of much dread. Variolation had by then been widely accepted; Jenner's vaccine was a way of providing the advantages of variolation without the risks either to the person inoculated or to his fellows (Miller, 1957). And there was no doubt that cowpox produced a much less severe disease than did variolation (Plates 6.1–6.3).

Vaccination was taken up with remarkable speed all over Europe and in the newly independent United States of America. It was, wrote Edward Edwardes (1902), "as if an Angel's trumpet had sounded over the earth".

S. WOOLNOUGH

Plate 6.10. The Jenner Museum. Edward Jenner bought The Chantry in Berkeley, Gloucestershire, in 1785 and lived in it until he died in 1823. The original cottage dates from 1384 at the latest. Purchased by the Jenner Trust in 1983, the building has been completely restored. The museum was opened on 10 May 1985 and commemorates Jenner, the development of the science of immunology, and the eradication of smallpox.

Effects of Introduction of Vaccination on Life Expectancy

Vaccination was the only public health measure of any importance that was newly and widely applied during the first quarter of the 19th century. It was enthusiastically accepted in France, where Napoleon gave it strong support, and in Sweden (see Fig. 6.1), two countries for which there were reasonably good vital statistics at that time.

During the early 19th century there was a vigorous controversy as to whether the human life span was fixed (a view supported by Thomas Malthus) or could be extended by public health measures, as the statistician Duvillard maintained (Westergaard, 1932). Data for life expectancy at birth before and after the introduction of vaccination supported Duvillard's view and illustrate what must be primarily the effect of vaccination on life expectancy.

Average Life Expectancy at Birth (in years)[a]

	France		*Sweden*	
	1795	*1817-1831*	*1791-1815*	*1816-1840*
Male	23	38	35	40
Female	27	41	38	44

[a] From Hishinuma (1976), rounded to nearest whole number.

Within 3 years of its publication in London, Jenner's *Inquiry* had been translated into German, French, Dutch, Italian and Latin (LeFanu, 1951). Jennerian vaccination was adopted much more rapidly and widely in Europe than variolation had been, and quickly spread around the world, gradually supplanting variolation where that had been practised. In London it was taken up immediately by William Woodville, Director of the London Small-Pox and Inoculation Hospital, and his colleague George Pearson, who in 1799 sent the vaccine, dried on threads, to some 200 physicians in England and to physicians in Paris, Berlin, Vienna, Geneva, Hanover, Portugal and North America. By 1800 vaccination was being practised in Constantinople, Paris and North America, and by 1801 in Moscow and Berlin; by 1802 viable vaccine had been shipped from Vienna to Bombay (Bowers, 1981). Additional challenge inoculations with smallpox, carried out in many places, confirmed Jenner's hypothesis that inoculation with cowpox virus provided protection against smallpox. In Boston, Benjamin Waterhouse (Plate 6.11) demonstrated protection in 7 persons in July 1800 (Blake, 1957) and in 1803, out of 17 000 vaccinations done in Germany, over 8000 had been tested by subsequent variolation (Dixon, 1962). In

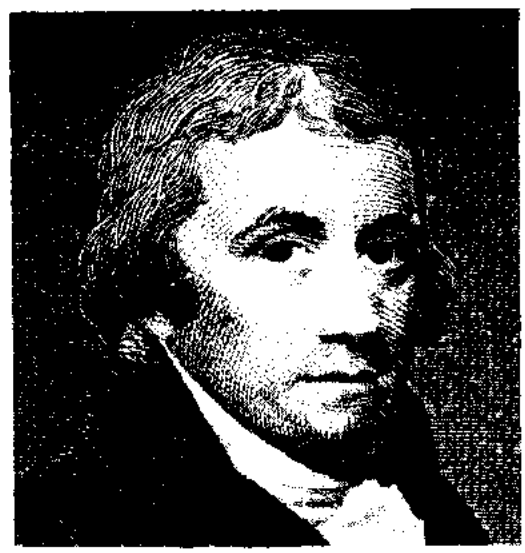

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Plate 6.11. Benjamin Waterhouse (1754–1846). The first professor of medicine in the United States of America, he carried out vaccinations in Boston in 1800 and interested President Jefferson in promoting vaccination. Portrait by Gilbert Stuart.

the USA, Waterhouse interested the then Vice-President, Thomas Jefferson, in the potential value of vaccination, and Jefferson immediately responded and enlisted the in-

Early Methods of Distributing Vaccine

From the earliest days of the development of vaccination it was clear that the most certain way of assuring that the vaccine was potent was to take material directly from a pustule—hence the importance of Jenner's demonstration that vaccine could be maintained by the arm-to-arm vaccination of children. The most famous exploitation of this procedure for the long-distance carriage of vaccine was the Balmis-Salvany Expedition, in which 20 orphans were carried on the ship to provide a succession of susceptible subjects for vaccination. However, more convenient methods were clearly needed.

Initially the commonest method was to impregnate threads with vaccine, much as thread impregnated with material from smallpox pustules had been used for variolation. Many of the early shipments between countries were made with such material. Another method was to spread the lymph on a glass slide and, when it was perfectly dry, cover it with a thin coat of mucilage of gum arabic (Paytherus, 1801). Silver or ivory lancets or points were also used, on which vaccine was allowed to dry; sometimes the liquid lymph on the ivory point was enclosed within a wax ball (Baron, 1838). In Great Britain the National Vaccine Establishment took over the responsibility for maintaining serial arm-to-arm transfers in 1808, and distributed several thousand preparations to physicians each year on ivory points or glass slides. Later, capillary tubes filled with glycerolated vaccine were used, but ivory points were still being employed in Great Britain as late as 1898.

With most species of virus all methods of transport except by direct transfer from pustule to arm would have been unsuccessful. However, the poxviruses are relatively so resistant to inactivation that these air-dried or wet preparations, maintained without refrigeration, often contained enough viable virus to produce a pustule in the vaccinated person. Nevertheless, failures did occur in the long-distance shipment of vaccine, as in Jenner's attempts to send material to India via the Cape, in several of the shipments from Great Britain to North America and in many shipments from Batavia to Japan.

terest of laymen and the medical profession in Virginia, Washington, Philadelphia and other places. In December 1801 he arranged for the vaccination of members of an American Indian delegation, supplying them with vaccine and with instructions from Waterhouse about its use (Halsey, 1936).

Perhaps the most dramatic demonstration of the readiness of the world for vaccination was the Balmis-Salvany Expedition commissioned by King Charles IV of Spain, which in 1803–1805 carried vaccine by the arm-to-arm vaccination of orphan children from Spain to the Spanish colonies in the New World, China and the Philippines (Fernández del Castillo, 1960; Smith, 1974; Bowers, 1981).

Early Problems with Vaccination

In spite of this remarkable record of acceptance, a variety of problems arose. Some of these were due to contamination of the cowpox material, some to shortage of material owing to the absence of infected cows and failure to maintain the virus in human subjects, some to theological and philosophical objections and some to Jenner's insistence that primary vaccination gave complete and lifelong protection against smallpox.

Contamination of cowpox material with variola virus

The first evidence of this kind of contamination came very early, from Woodville and Pearson, who had embarked on vaccination at the London Small-Pox and Inoculation Hospital. In January 1799 cowpox was discovered at a dairy at Gray's Inn Lane, and Woodville collected lymph from lesions on one of the milkmaids. With this he vaccinated cases at the Small-Pox and Inoculation Hospital and about two-thirds of some 500 subjects had a generalized eruption. Subsequently Woodville (1800) realized that this was due to cross-infection or contamination with material from smallpox cases, and noted that a generalized eruption did not occur when persons were vaccinated in private houses. Material from some of the hospital patients was widely distributed by Pearson (Baxby, 1981), and Razzell (1977a) has suggested that it consisted of attenuated strains of

variola virus which constituted the source of vaccinia virus. This hypothesis is not supported by biological evidence (see Chapter 2), but the origin of vaccinia virus, the agent used for smallpox vaccine throughout the latter part of the 20th century, is still uncertain (Baxby, 1981).

Viral contamination has been a recurrent, usually unrecognized, problem. During the latter part of the 19th century it was often decided that vaccine produced by repeated arm-to-arm transfer or maintained in cows needed to be enhanced in potency. As well as "humanized lymph" being passed from man back to the cow ("retrovaccination"), cows were inoculated with variola virus from cases of smallpox. Many of the best-known strains of vaccinia virus were purported to have been derived from smallpox cases in this way (see Copeman (1899) and Chapter 11). However, the environment of vaccine lymph institutes was heavily contaminated with vaccinia virus, as Kelsch et al. (1909) showed, when cows in such an institute which had been inoculated in the scarified skin with glycerol on its own developed a few vaccinial vesicles a few days later. Carefully performed experiments in modern times have failed to "transform" variola to vaccinia virus (Nelson, 1943; Herrlich et al., 1963; Dumbell & Bedson, 1966).

Contamination of human lymph

With the separation of vaccine maintenance and preparation from the smallpox hospitals, the problem of contamination with variola virus was overcome, but other kinds of contamination posed problems. While arm-to-arm vaccination provided a simple means of maintaining a source of virus, it introduced the possibility of the transfer of other human diseases, especially erysipelas and syphilis and, although usually unrecognized, hepatitis B. The etiology and epidemiology of the last-named disease were quite unknown at that time, but in a remarkably percipient paper Lürman (1885) concluded that an epidemic of 191 cases of jaundice among some 1200 employees in a factory in Bremen, Germany, in 1883–1884 was probably associated with the mass vaccination of the staff with a particular batch of humanized glycerolated lymph.

The danger of vaccinal syphilis was recognized in Italy as early as 1814, and soon after that in other countries. Particularly dramatic was an episode at Rivalta, Italy, in 1861, in which 44 out of 63 children

Jenner's Critics

Jenner was not without faults or without critics. His principal biographer, Baron (1838), was adulatory in his attitude; Creighton (1887, 1889) was violently condemnatory and Crookshank (1889) mildly critical. More recently, Razzell (1977a) entered the controversy with a book entitled *Edward Jenner's Cowpox Vaccine: the History of a Medical Myth*, to which Baxby (1981) has produced a rejoinder.

Many of the specific comments made by these and other critics have some substance. Both Creighton and Crookshank were particularly critical of Jenner's adoption (in the published paper of 1798 but not in the draft submitted earlier to the Royal Society) of the term "variolae vaccinae"—cow smallpox—which they held was a false name, designed to mislead. Creighton could see no value in Jenner's contribution, except in so far as it led to Woodville's vaccine, and could discern many disadvantages, especially the danger of transmitting syphilis by arm-to-arm vaccination. Razzell holds that the material used for vaccination, at least after Jenner's original experiments, was not derived from cowpox but was an attenuated strain of variola virus and thus vaccination was really an extension of variolation.

This is not the place to adjudicate on these controversies; Baxby (1981) discusses them at length. It seems to the present authors that, whatever its shortcomings and Jenner's failings, publication of the *Inquiry* and the subsequent energetic promulgation by Jenner of the idea of vaccination with a virus other than variola virus constituted a watershed in the control of smallpox, for which he more than anyone else deserves the credit.

vaccinated with material from a child with unrecognized syphilis acquired overt syphilis; several died and some infected their mothers and nurses. Grön (1928) lists several other episodes, and Creighton (1887), a particularly bitter critic of Jenner, even suggested that "the real affinity of cowpox is not to the small-pox but to the great pox".

Shortages of cowpox virus

For reasons which have only recently become apparent (see Chapter 29), cowpox, as a disease of cows, was a sporadic disease, as Ceely (1842; quoted in Crookshank, 1889) accurately described. It was very rare in certain parts of Great Britain and some other countries of Europe, and its occurrence from year to year varied unpredictably. Thus it was not always easy to have access to a cow with lesions at the right stage for the direct vaccination of man. Jenner recognized this problem and sought to overcome it by using arm-to-arm vaccination, a method that was widely adopted (see Plate 6.14A). Arm-to-arm vaccination continued to be practised in England until 1898, when it was banned, as far as public vaccinations were concerned. But it was not always possible to maintain a chain of infection in children, so that recourse to animal sources was still necessary. Further, the potential problem of vaccinal syphilis was still present, if human sources were used for vaccination. Another problem was that vaccine was thought to lose effectiveness after having been maintained for a prolonged time by arm-to-arm vaccination (Ballard, 1868).

One alternative source recommended by Jenner was material from the lesions of horses suffering from a disease called "grease". This is an inflammation of the fetlocks and is caused by a variety of agents, a rare one being horsepox virus, which usually produces lesions on other parts of the body (face, vulva) as well (Crookshank, 1889; see Chapter 2, Plate 2.15). Loy (1801) demonstrated that virus obtained from lesions on the hand of a man who had been treating horses suffering from grease, and material obtained directly "from a sore in the heel of a horse with the Grease", produced typical vaccine lesions in children and lesions like cowpox on the teats of inoculated cows. He showed that children inoculated with this material resisted variolation.

In 1817, equine virus supplied to the National Vaccine Establishment was widely distributed in Great Britain (Baron, 1838), and horsepox was also used as a source of vaccine in continental Europe. Chaveau (1866) believed that in any case horsepox was caused by the same virus as cowpox, although it was an even less common disease.

Production of vaccine in calves

For some time "retrovaccination" was practised, a procedure that consisted in taking the virus from human lesions back to the cow, which was then used as a source for further arm-to-arm vaccination. This was done primarily to maintain the potency of the vaccine, rather than providing a source of vaccine for distribution and use. The use of animals as a method of vaccine production on a large scale, which overcame problems of vaccinal syphilis and of the loss of vaccine sources, was developed in Italy, which had long shown an interest in vaccination. As early as 1805 Troia

Horsepox as a Source of Vaccine Lymph

In 1817 Jenner appears to have replaced vaccination by "equination" and stocks of virus from cases of horsepox were supplied to the National Vaccine Establishment and widely diffused. Crookshank (1889) concludes a long commentary on horsepox as follows: "In this country, it is more than probable that some of Jenner's stocks of equine lymph are still in use; but equination is not wittingly practised, for it is commonly supposed that all the lymph employed for the purposes of vaccination has been derived from Cow Pox. In France, on the other hand, it is extensively employed. M. Larget informed me that at the Animal Vaccine Station at Bordeaux the lymph which gave most satisfaction was derived from the horse, and that he had been able on two occasions to renew his stock from equine sources."

Plate 6.12. Wood engraving from *Harper's weekly*, 23 April 1870, showing a general vaccination day at the Paris Academy of Medicine. Arm-to-arm vaccination had been superseded by vaccination from the cow after the discussions of the Medical Congress of Lyons in 1864.

in Naples was employing calves as a source of human vaccine, and Galbiati (1810) continued the practice. Then in 1840 Negri in Naples carried the virus continuously in calves.

Use of the calf as a source of vaccine appears to have been confined to Italy until the Medical Congress of Lyons in 1864, when there was heated criticism of vaccination on the grounds that the method of maintenance and production of vaccine then practised in France—namely arm-to-arm vaccination—carried a serious risk of transmitting syphilis. In this discussion, Dr Viennois and Professor Palasciano spoke about the calf as a source of virus, as practised in Italy (Congrès Médical de Lyon, 1864). Dr Chambon and Dr Lanoix immediately arranged for the delivery of a calf incubating vaccinia to be sent to Paris from the Neapolitan Institute and henceforth the use of calf vaccine gradually extended through France (Depaul, 1867). Belgium adopted it in 1865, and by 1884 the German Royal Commission on Vaccination recommended it in Germany (Hime, 1896). The Netherlands and many states of the USA followed suit. Great Britain was one of the last countries to adopt the practice. Its use there was initiated in 1881, but arm-to-arm vaccination continued to be popular until it was finally banned in 1898 (Table 6.3; Dudgeon, 1963). As late as 1896 Hime felt obliged to devote considerable effort to justifying the practice of "animal vaccination".

The manner of inoculation consisted in making multiple insertions on a shaved area

Table 6.3. Record of vaccine lymph issued by the National Vaccine Establishment, Great Britain[a]

	1881	1882	1898	1899 (to March)
Human lymph:[b]				
Ivory points	10 260	8 193	0	0
Glass slides	440	40	0	0
Capillary tubes	21 118	25 572	3 739	0
Calf lymph:[b]				
Ivory points	470	975	20 317	0
Capillary tubes	30	95	105	125 038

[a] Based on Dudgeon (1963).
[b] For an explanation of the methods of distribution, see box earlier in this chapter.

on the skin of a calf (Plate 6.13), vaccine being reaped from the separate pocks found at each insertion site on the 5th day after inoculation by expressing the fluid and, as Hime (1896) recommended, scraping the surface of the pock. The material expressed was ground in a mortar and suspended in glycerol, a practice embarked on empirically in Italy in Negri's day, and supported by Koch in Germany. In Great Britain considerable credit was given to Copeman (1899; see also McNalty, 1968), who demonstrated that glycerol was not only a convenient fluid for suspending vaccine, in terms of its clarity and its viscosity, but was also bactericidal though not virucidal (Copeman, 1892).

An important feature of the first hundred years of vaccination was that vaccine production was conducted without any sort of state control. "Vaccine parks" were established by all and sundry, individual physicians maintained their own stocks of "humanized" vaccine by arm-to-arm inoculations, and Hime (1896) complained "The country [Great Britain] is flooded with cheap stuff 'made in Germany' and elsewhere, of unknown nature or origin. It is cheap and therefore sells." In Great Britain the labours of the Royal Commission on Vaccination (Great Britain, 1898) resulted in the Vaccination Act of 1898, which prohibited arm-to-arm vaccination by public vaccinators and undertook to supply them with glycerolated calf lymph. However, it was not until 1925 that regulation of the quality of vaccine was firmly established with the promulgation of the Therapeutic Substances Act (Hutchinson, 1946).

Theological and philosophical objections

Some churchmen had taken strong positions in controversies about variolation, both for and against. It was much the same with vaccination. In Italy, priests led processions of people to vaccination sites to be vaccinated; in Bohemia village priests reminded parents of their responsibility not to neglect the vaccination of their children, and in Germany, Great Britain and Switzerland some clergymen vaccinated people themselves. Vaccination was endorsed by the Pope during an epidemic of smallpox in Rome in 1814.

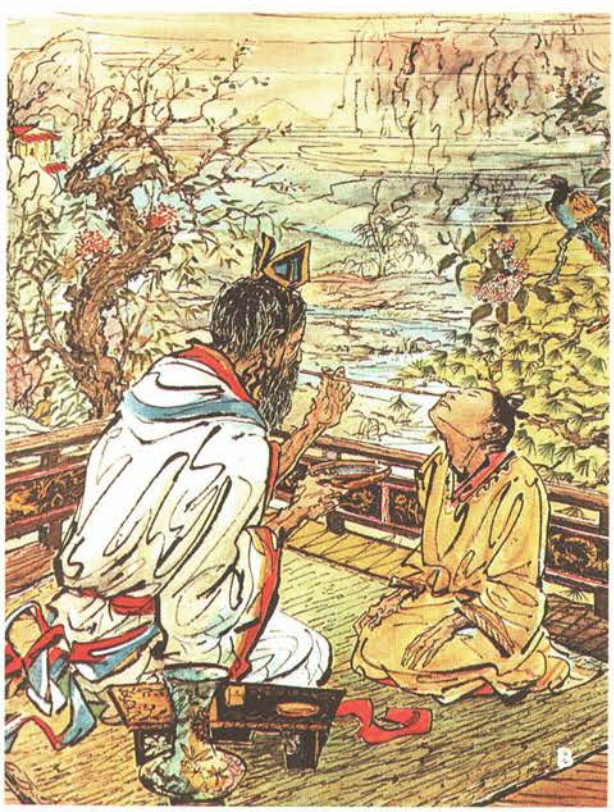
Plate 6.13. Production of vaccine in calf, 5 days after inoculation. (From Depaul, 1867.)

On the other hand, some members of the Church raised objections that vaccination was interfering with the will of God and that smallpox was sent to chasten the population. There were objections to the inoculation of humans with a disease of animals, and popular cartoons depicted people growing horns or tails after being vaccinated (Plate 6.15B).

More serious philosophical objections emerged from the mid-19th century onwards, especially in Great Britain, when efforts to make vaccination compulsory conflicted with growing sentiments favouring personal freedom of choice. Before the era of bacteriology, there was no generally accepted scientific basis for the theory of infection by contagion. Anticontagionists and anti-vaccinationists tended to be liberal re-

MUSÉE DE LA CHARTREUSE

Plate 6.14. A: Arm-to-arm vaccination, as practised in Europe. Painting by Charles Desbordes, "La Vaccine", 1822. **B:** Insufflation of powdered smallpox scabs by the intranasal route, as practised with variola virus in China.



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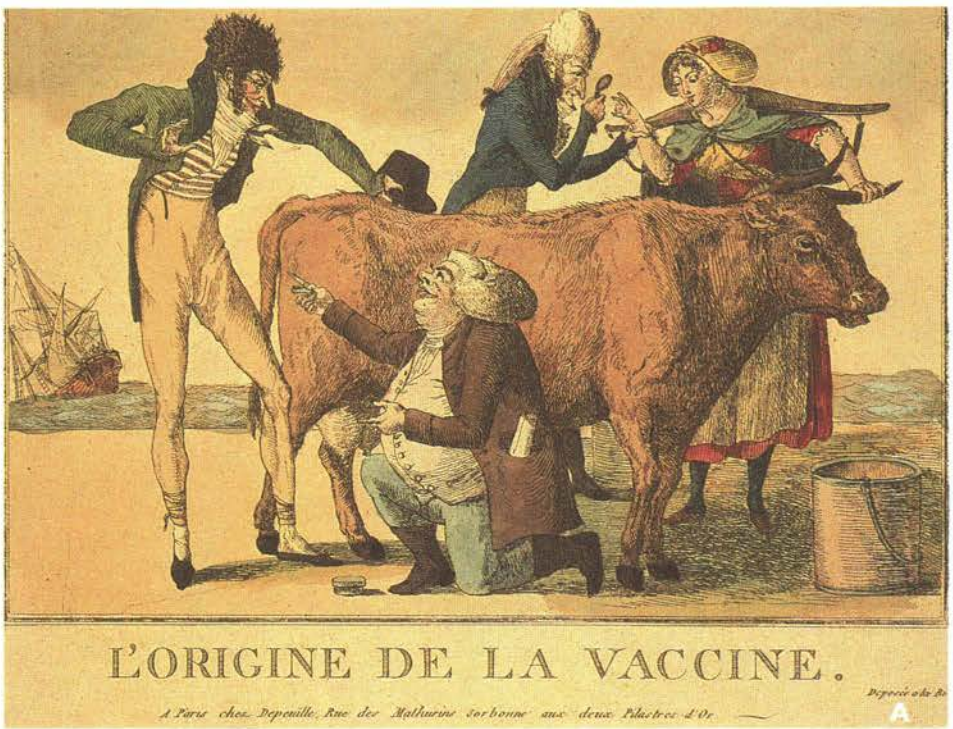

Plate 6.15. **A:** French engraving, *c.* 1800, depicting the newly discovered process of vaccination. **B:** English engraving by James Gillray, 1802, reflects the scepticism with which vaccination was received initially in some quarters.

formers who fought for individual freedom against what they saw as despotism and reaction; both quarantine and vaccination were equated with the restrictions of unheeding officialdom.

Although Parliament in Great Britain was slow to introduce legislation on vaccination, possibly because of the belief that it was important that the poor should not be protected at public expense (Chase, 1982), and because of liberal antivaccinationist sentiment, firm action was taken quite early in several other European countries. Vaccination was made compulsory in Bavaria in 1807,

Resistance to Compulsory Vaccination in Great Britain

"The Vaccination Acts of 1840, 1841 and 1853 ... made [vaccination] successively universal, free, non-pauperising and, finally, compulsory. The Acts of 1861, 1867 and 1871 made vaccination enforceable by the appointment of Vaccination Officers, and finally compelled enforcement by making such appointments mandatory ... the Act of 1867 permitted parents to be fined repeatedly until the child was vaccinated ... the Act of 1871 ... made negligent parents liable both for non-compliance with the Act and for disobedience of a court order. In default of fines and costs, parents were sometimes committed to gaol and household goods were distrained for sale. As incidents of bona fide opposition to vaccination arose, the severity with which the law was enforced and the weight it laid upon the poorer classes attracted more attention. Gradually, individuals found organised means of expressing their discontent. Such opposition merged with the rising tide of working-class opinion and with the efforts of radical reformers who saw in the vaccination question the embodiment of impersonal and uncompromising governmental intervention in the daily life of the individual ... Sanitary reformers of the era were largely united in the belief that enforced 'cleanliness' was a prerequisite to social 'godliness' and a sufficient defence against disease and while many accepted vaccination as a useful, ancillary instrument of prevention, they could not agree with the implicit assumption of 'specificity', and were reluctant to see it impede or replace the elimination of foul air, overcrowding and filthy streets.

"The [subsequent] development of the antivaccinationist movement can be seen in five distinct phases. First, sporadic Radical outbursts in London and the North led during the seventies to the formation of the Society for the Suppression of Compulsory Vaccination in London ... The second phase of activity, under the Cheltenham National Anti-Compulsory Vaccination League, extended the movement to the rural population and the agricultural middle classes. When League intrapolitics and its limited programme failed to make an impact on national opinion, a more extensive campaign was begun. This came about in the third phase, with the establishment of a new London Society for the Abolition of Compulsory Vaccination. The highly co-ordinated pressure group tactics of this Society unified support and helped to secure Government inquiry into the vaccination question. The actions of this group in the period 1880–89 prepared the ground for the fourth phase which emerged in the nineties, when the London Society, using the Report of the Royal Commission on Vaccination as a manifesto, amalgamated antivaccinationists into a new National Anti-Vaccination League, and pressed for remedial legislation. The fifth phase, beginning in reaction to administration abuse of the conscientious objection provision of the 1898 Act, receded with the League's decline after 1907, when its final objectives were essentially achieved.

"In retrospect, the movement was part of a wider public reaction against the advance of 'new science' and scientific medicine. Fear, distrust and the human tendency to cherish 'natural' methods of treatment and 'sanitary' methods of prevention could be overcome only by educational means. This required the active co-operation of physicians and lawyers in supervising the administration of compulsory law which had, historically, been accepted naively by Parliament. This co-operation was noticeably absent at this critical interface of law, medicine and public opinion." (MacLeod, 1967.)

in Denmark in 1810, in Bohemia in 1812, and in Sweden in 1816.

Duration of immunity following vaccination

Jenner is regarded as the father of immunology, but it would be a mistake to believe that he interpreted the resistance to smallpox conferred by vaccination as an immunological phenomenon, as now understood. Rather he saw it as a change in the constitution that rendered an individual resistant to smallpox forever. Jenner maintained this belief until he died in 1823, and explained the increasing number of cases that occurred as time passed since vaccination as being due to "imperfect" vaccination with "spurious cowpox", or for some other reason. Jenner was right in noting that pock-like lesions on the teats of cows could be due to agents other than cowpox (see Chapter 29) but wrong in believing that immunity to smallpox was absolute and lifelong. Jenner's fallibility on this issue was exploited by antivaccinationists opposed to all vaccination, until revaccination provided the solution.

Recognition of the need for revaccination came much earlier in continental Europe than in Great Britain, where the official attitude throughout the 19th century was that vaccination in infancy gave lifelong protection. Thus, in Great Britain the 1840 legislation providing for infant vaccination, and subsequent Acts providing for compulsory infant vaccination, were founded on the false Jennerian concept that infant vaccination produced lifelong immunity, so that revaccination was unnecessary. As late as 1898 the Royal Commission on Vaccination (Great Britain, 1898) stated that only in very exceptional circumstances did infant vaccination not give lifelong protection.

On the continent of Europe and particularly in Germany, the need for revaccination was recognized early, with dramatic results in countries in which revaccination was compulsory (see Table 6.4).

Evidence for the Efficacy of Vaccination

The initial response to the idea of vaccination was based on an optimistic extrapolation of Jenner's meagre experimental results, its close resemblance to variolation, in principle and in the production of a local lesion, and the deeply felt need to find something better than variolation, which usually brought on a severe disease and could cause outbreaks of smallpox in uninoculated contacts. This is well expressed in a letter dated 2 August 1798 from Cline, who performed the first vaccination in London, in July 1798, to Jenner (Baron, 1838):

> "I think the substituting of cow-pox poison for the small-pox promises to be one of the greatest improvements that has ever been made in medicine: for it is not only so safe in itself, but also does not endanger others by contagion, in which way the small-pox has done infinite mischief. The more I think on the subject the more I am impressed with its importance."

After Jenner's initial publication in 1798, Woodville and Pearson in London and others in Germany, Italy and the USA lost no time in carrying out challenge inoculations that far exceeded in number those that Jenner had performed. Then followed growing experience of the immunity of vaccinated persons to natural smallpox. Because of its very obvious advantages, and because it built on the practice of variolation, established in Europe and the Americas for some 80 years, vaccination was adopted throughout the world—and very rapidly. For example, Jenner stated that by 1801 over 100 000 persons had been vaccinated in Great Britain, whereas by 1730, 8 years after the introduction of variolation, less than 1000 people had been variolated in Great Britain and North America.

As more and more people were vaccinated, smallpox mortality declined dramatically and for some decades remained low. Such epidemics as did occur were less severe and less frequent than in the 18th century. Where good statistics were kept, as in Geneva (Perrenoud, 1980) and Denmark and Sweden (Moore, 1817), it was seen that the numbers of reported deaths from smallpox fell to unprecedently low levels. Not only did the morbidity and mortality decline dramatically, but the cases that did occur were almost always in unvaccinated persons. There was no logical explanation for this change except the introduction of vaccination.

Faced with this evidence, the governments of several countries decided that protection against smallpox was not something that could be left to individual choice. First, variolation, as a potential source of smallpox, was banned in Russia in 1805, in Prussia in 1835 and in Great Britain in 1840 (Edwardes,

1902). Then vaccination, usually of infants, was made legally compulsory in Bavaria (1807), Denmark (1810), Norway (1811), Bohemia and Russia (1812), Sweden (1816) and Hanover (1821). Great Britain and France were to follow much later, in 1853 and 1902 respectively. Of course, having a law on the statute books and enforcing it were two different matters, especially as the problem of the large-scale production and distribution of vaccine was not solved until the latter half of the 19th century. Nevertheless, the evidence for the efficacy of vaccination, provided by countries in which it was compulsory and in which the law was enforced, was compelling. Edwardes (1902) summarized much of this evidence in his excellent little monograph.

The figures for Sweden, which has some of the earliest reliable statistics, are shown in Fig. 6.1. Vaccination began in Sweden late in 1801 and was made compulsory in 1816. From about 1802 onwards there was a dramatic change in the 18th century pattern of major epidemics (3000–7000 smallpox deaths per million population) every 5 years or so, against a background of high endemicity (600–800 smallpox deaths per million population). The epidemic waves subsided and from about 1810, as vaccination became more widespread, the figures fell to unprecedently low levels. Six years after the institution of compulsory vaccination the ratio of smallpox deaths per million population reached a single figure—over a hundredfold reduction from the previous endemic level. After that, in spite of the maintenance of a reasonably high level of infant vaccination, the death rate rose again and epidemics recurred, although at a tenth the amplitude and at longer intervals than in the 18th century.

This pattern occurred elsewhere in Europe, wherever vaccination coverage was reasonably good. After a period of freedom for some 20 years, smallpox began to recur in pandemics affecting most of Europe in 1824–1829 and 1837–1840, with mortalities that were low by 18th century standards but much higher than the general public or the health workers of the time regarded as tolerable. Further, the pattern of the epidemics had changed. During the 18th century the high level of endemicity had ensured that most adults living in cities were immune as a result of childhood infection or perhaps of variolation; urban epidemics occurred primarily in children. Now, where

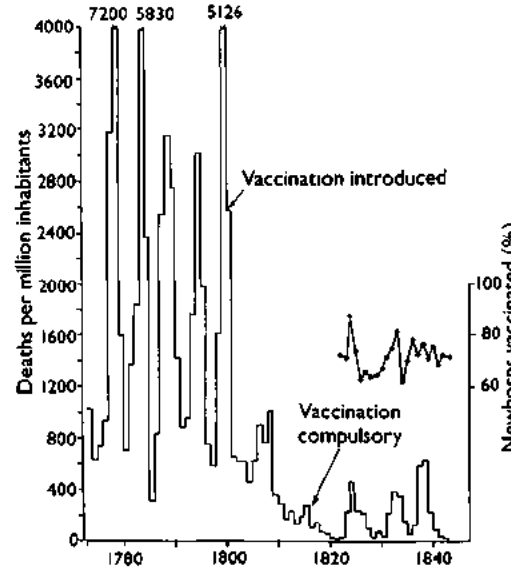

Fig. 6.1. Smallpox deaths per million population in Sweden between 1722 and 1843, showing from 1820 onwards the proportion of newborn children who were vaccinated in infancy. (Based on Edwardes, 1902.)

infant vaccination was widespread, there was a higher rate of illness in adults than in children. And even more than in the past, smallpox deaths occurred among the lower classes of society, who had less access to vaccination.

It was clear that Jenner's belief that one inoculation with cowpox gave permanent protection against smallpox was wrong. An increasing number of cases occurred in vaccinated adults, but with a much lower case-fatality rate than before, and a different and milder symptomatology, which caused difficulties in diagnosis (Monro, 1818). One suggested answer, in Great Britain, was to revive variolation (Creighton, 1894). A safer, more sensible, solution was to recommend revaccination. The German states took the lead, and revaccination was introduced in Württemberg in 1829; other states, beginning in 1833, instituted the compulsory vaccination of military recruits. In the Prussian army, the number of deaths from smallpox, which had averaged 88 per year in 1831–1834, dropped to single figures and averaged less than 2 per year for the next 30 years.

The great European epidemic of 1870–1871 (see Chapter 5) provided a salutary lesson that smallpox was not yet under control, but the very much lower incidence in

the Prussian than in the French army demonstrated the value of vaccination and revaccination. Germany took these lessons to heart and in 1874 promulgated a vaccination law requiring that every child should be vaccinated during the 2nd year of life and that every schoolchild should be revaccinated during the 12th year, unless an attack of smallpox, or a successful vaccination, had occurred within the previous 5 years. The results, when compared with the prevailing situation in Austria, in which general conditions were similar but revaccination had not been introduced, were dramatic (Table 6.4) and hardly require comment.

A hundred years after Jenner's experiment with James Phipps, the *British medical journal* (1896) published a Jenner memorial number and medical journals in many other countries published special articles on Jenner and vaccination (Pfeiffer, 1896; *Index medicus*, 1897). Russian translations of all of Jenner's publications on vaccination were also produced in 1896 (LeFanu, 1951).

A few years later Edwardes (1902) published his compendium of statistics. All investigations illustrated that the practice of vaccination and revaccination, properly conducted, was a brilliant success; Jenner's prediction (see Plate 6.8) that smallpox could be eradicated by vaccination was correct. Almost 80 years were to elapse, however, before *global* eradication was achieved, and practices additional to mass vaccination, which in an elementary form had antedated the concepts of variolation and vaccination, had to be invoked—namely, isolation and containment.

CONTROL BY ISOLATION AND QUARANTINE

One other method of control began even before variolation and, combined with vaccination, furnished the ultimate method for the control of smallpox—namely, isolation and, for travellers by sea, its equivalent, quarantine. It was believed from early times, first with leprosy and then with plague, that it might be possible to avoid certain diseases by ensuring that no contact occurred between

Table 6.4. A comparison between the number of smallpox deaths per million population in German states before and after the German vaccination law of 1874 (compulsory vaccination and revaccination) and in Austria (in which only primary vaccination was practised), during the same period[a]

Year	Prussia	Bavaria	Württemberg	Austria
1866	620	120	133	368
1867	432	250	63	484
1868	188	190	19	370
1869	194	101	74	374
1870	175	75	293	293
1871	2 432	1 045	1 130	383
1872	2 624	611	737	1 866
1873	356	176	30	3 094
1874	95	47	3	1 725
1875	36	17	3	576
1876	31	13	1	406
1877	3.4	17	2	555
1878	7.1	13	0	631
1879	12.6	5	0	534
1880	26	12	5.6	674
1881	36.2	15	3.6	807
1882	36.4	12	6.6	947
1883	19.6	6	35.2	596
1884	14.4	1	11.6	530
1885	14	3	0	600
1886	4.9	1	1	400
1887	5	1.8	0	417
1888	2.9	3.8	0.5	615
1889	5.4	5.2	0	537
1890	1.2	1.5	0	249
1891	1.2	1.2	0	287
1892	3.0	0.5	0	256
1893	4.4	0.7	1	244
1894	2.5	0.3	0	105
1895	0.8	0.2	0	49
1896	0.2	0.2	0	36
1897	0.2	0	0	61

[a] Based on Edwardes (1902).

diseased and healthy persons. The practice of designating huts or villages in which severe infectious diseases such as plague or smallpox were present, as an indication that they were to be avoided, appears to have arisen independently among several different peoples in Africa, Asia and Europe. It was difficult to achieve the efficient isolation of cases where diseases were endemic, but relatively easy when they were present on ships that approached disease-free ports. Thus the quarantine of ships developed earlier and more effectively than did effective isolation of smallpox patients on land.

The scientific underpinning of the concepts of isolation and quarantine had to await the enunciation of the germ theory of infectious diseases by Pasteur and Koch, in the latter half of the 19th century, but long before this a belief had developed that such diseases were spread by contagion. The best-known early European exponent of this view, for smallpox and measles, was Girolamo Fracastoro of Verona (1478–1553). In a classic book (Fracastoro, 1546) he attributed these diseases to specific seeds, or seminaria, which were spread by direct contact from person to person, by intermediate objects, or fomites, or perhaps at a distance, through the air.

Quarantine for Shipping

At the time of the Black Death, in the 14th century, the Venetians and other trading nations of the Mediterranean recognized that ships sometimes brought plague to their cities, and instituted the practice of isolating travellers and ships suspected of carrying plague for a period that became, after some adjustments, 40 days—hence the word quarantine (Gerlitt, 1940).

The idea of using quarantine to prevent the entry of smallpox came most readily to European colonists in places previously free of smallpox, notably North America and Australia. Smallpox was endemic in Great Britain when North America was being settled in the early part of the 17th century, and smallpox occurred on several ships during the Atlantic crossing. Later, epidemics of smallpox occurred in Boston, the major seaport at the time, in 1636, 1659, 1666, 1677–1678, 1689–1690 and 1697–1698. Between these times the disease disappeared; the introductions followed the arrival of ships carrying new settlers or slaves with smallpox.

Although the early North American settlers believed no less than their British contemporaries in the notion of pestilence as divine punishment, they were pragmatic enough to invoke quarantine to prevent the entry of smallpox from overseas. By 1647, vessels arriving in Boston from the West Indies with infected passengers or crew were quarantined in the harbour, initially probably for yellow fever (Blake, 1953, 1959), and similar measures were subsequently adopted in New York and other port cities (Tandy, 1923).

Eventually, as the European settlements in North America increased in size, smallpox became endemic and quarantine was no longer relevant. Variolation and subsequently vaccination became more important ways of controlling smallpox. But in Australia and New Zealand, much more sparsely populated and situated much further from other centres of population than North America, smallpox never became endemic and quarantine remained an important method of excluding the disease throughout the 19th and 20th centuries (Cumpston, 1914; see also Chapter 8).

Isolation of Cases

The isolation of patients on land was more difficult to put into effect than preventing the landing of infected persons from ships. Nevertheless, the colonists in North America attempted this as early as 1662, when an order was issued at East Hampton, Long Island, to prevent the spread of smallpox from local Indians to the town's population (Tandy, 1923). In 1667 the colony of Virginia legislated for the mandatory isolation of victims of smallpox at home.

The idea of isolation to control the spread of smallpox received a considerable stimulus with the popularization of variolation, since it was early recognized that one of the risks of this practice was the spread of smallpox to uninoculated contacts. It therefore became customary to variolate children in groups and keep them in isolation, tended by persons who had already had smallpox, until the scabs fell off. Jenner himself had this experience in 1757, at the age of 8 (Baron, 1838).

By the end of the 18th century some writers had already conceived the idea of controlling smallpox by a combination of variolation on a wide scale and the isolation of smallpox

patients. Haygarth (1793) developed a comprehensive plan involving the periodic variolation of the general public, the isolation of cases, the disinfection of fomites, etc.; a few years later Carl (1799), then Director of the Inoculation Institute in Bohemia, proposed a similar procedure. By 1803 the government of Bohemia required the compulsory notification of cases of smallpox, the isolation of cases and the sterilization or destruction of bed-linen, toys, etc., of smallpox patients (Carl, 1802; Raška, 1976).

Impressed by the example of the "stamping out" of the devastating cattle plague, rinderpest, in Great Britain a few years earlier, Sir James Simpson, famous for his introduction of chloroform for anaesthesia, wrote an article for the *Medical times and gazette* in 1868 (Simpson, 1868), which aroused considerable interest and discussion. In it he developed a proposal for eradicating smallpox and other infectious diseases, such as scarlet fever, measles and whooping-cough, by the isolation of cases. He recognized that his proposals could be most readily achieved with smallpox, because vaccination provided a means of protection for nurses and others who had to remain in contact with patients. His proposed "Regulations" were as follows:

"1st. The earliest possible notification of the disease after it has broken out upon any individual or individuals.

"2nd. The seclusion, at home or in hospital, of those affected, during the whole progress of the disease, as well as during the convalescence from it, or until all power of infecting others is past.

"3rd. The surrounding of the sick with nurses and attendants who are themselves non-conductors or incapable of being affected, inasmuch as they are known to be protected against the disease by having already passed through cow-pox or small-pox.

"4th. The due purification, during and after the disease, by water, chlorine, carbolic acid, sulphurous acid, etc., of the rooms, beds, clothes, etc., used by the sick and their attendants, and the disinfection of their own persons."

Perhaps the most vigorous advocacy of isolation as a method of controlling smallpox was developed in the city of Leicester, in England, largely as a result of the strength of the local antivaccinationist movement (Fraser, 1980). The essentials were the prompt notification of cases of smallpox, the isolation of cases in the town's Fever and Smallpox Hospital, and the quarantine of all immediate contacts, with compensation for loss of time from work. Vaccination was not mentioned, and in Leicester there was strong disapproval of compulsory vaccination, and especially of the prosecution of those who refused vaccination on grounds of conscientious objection, until the turn of the century. The system was developed during the 1870s and achieved notoriety in the 1890s. Subsequently, the vaccination or revaccination of contacts was added to the routine procedure (Millard, 1914). This procedure, the "Leicester method" plus vaccination, like the proposals of Haygarth and Carl long before, anticipated the surveillance and containment strategy of the World Health Organization's Intensified Smallpox Eradication Programme.

The Establishment of Smallpox Hospitals

Dixon (1962) devotes a chapter of his book to the smallpox hospital and traces the history of such hospitals in Great Britain, as well as outlining his views on basic requirements. The notion that a special infectious diseases or smallpox hospital or ward should be an integral part of the control of smallpox arose as recently as the 20th century, except for a

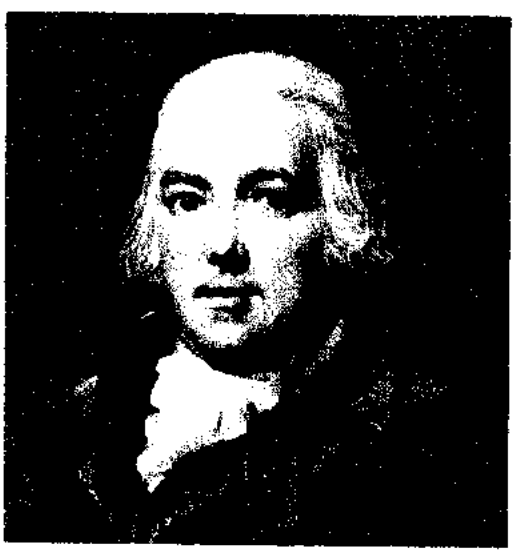

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Plate 6.16. William Woodville (1752–1805). Director of the London Small-Pox and Inoculation Hospital at the time of publication of Jenner's *Inquiry*. Many of his early vaccinations, carried out in the presence of cases of smallpox, were associated with generalized rashes, a source of confusion until they were recognized as being caused by variola virus.

few places, such as Leicester (see above), in which such institutions already existed. Prior to that, hospitals were sometimes established in response to epidemics, often of smallpox, as in Quebec in 1639 (Hôtel Dieu) and on frequent occasions in towns in Great Britain. But in general smallpox patients were not admitted to hospitals.

In England, the London Small-Pox and Inoculation Hospital was founded in 1746, initially for the treatment of poor persons with smallpox but soon afterwards mainly as a hospital for subjects undergoing variolation. An Inoculation Institute was established in Brno (Bohemia) at about the same time. Subsequently small private "inoculation hospitals" were set up in most places in which variolation was practised extensively, to prevent the spread of smallpox to susceptible contacts. The London Small-Pox and Inoculation Hospital played an important role in the early days of vaccination, for Woodville worked there (Plate 6.16) (Woodville, 1796, 1799, 1800).

Long before this, the Japanese book *Ishinho*, produced in AD 982, mentioned the establishment of special hospitals for smallpox cases, but it is difficult to interpret their significance. The use of infectious diseases hospitals as part of the machinery for controlling smallpox required an efficient system of notification, which was easier for smallpox than for most other diseases. Notification formed the core of the "Leicester method" and was a most important factor in limiting the spread of smallpox after importations into Europe and North America during the 20th century (see Chapter 23). However, national notification of cases of infectious diseases was not introduced into Great Britain, for example, until 1899, and even an imperfect system of notification required a public health service far more effective than anything that existed during the 19th century. Even in the industrial countries of Europe, therefore, elimination of smallpox was not achieved until well into the 20th century (see Chapter 8).

CHAPTER 7

DEVELOPMENTS IN VACCINATION AND CONTROL BETWEEN 1900 AND 1966

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INTRODUCTION

By the year 1900 vaccination was in widespread use throughout the industrialized countries as well as in some cities in what were then the colonies of various European powers. Although variolation was no longer practised in Europe and North America, it was still widely employed in many parts of Africa and Asia. Smallpox persisted as an endemic disease in virtually every country of the world (see Chapter 8, Fig. 8.16), although its incidence in the industrialized countries was lower than in previous centuries.

The latter half of the 19th century saw the emergence of microbiology and immunology as scientific disciplines. Because of their familiarity with vaccination, many of the pioneers in these new sciences used vaccinia virus for their studies (see Chapter 2). In consequence, the empirical practices of Jenner and his early followers were placed on a more scientific basis. Vaccine production was no longer the province of the local physician, who had maintained the virus by arm-to-arm transmission, and small local "vaccine parks", but was taken over by factory-type laboratories, the precursors of the great bio-

Cowpox Virus and Vaccinia Virus

All orthopoxviruses exhibit cross-protection in laboratory animals. Among the orthopoxviruses that infect humans, cowpox and vaccinia viruses usually produce only local lesions, with minimal systemic disturbance, whereas variola and monkeypox viruses cause serious systemic diseases. Jenner's original "variolae vaccinae" was cowpox virus, and during the 19th century, on many occasions, virus for vaccination was derived from lesions in cows and sometimes horses in several European countries. Since the description of the biological characteristics of cowpox virus by Downie (1939a,b), it has been recognized that smallpox vaccines in use then, and probably for many years before the 1930s, consisted not of cowpox virus, but of another orthopoxvirus which had long been called "vaccine virus", but was shown by Downie to have biological properties different from those of cowpox virus (see Chapter 2). Although some smallpox vaccines were still said to be made from cowpox virus during the 1960s, it is doubtful, in the light of evidence from contemporary virological studies, whether this was so.

The origins of vaccinia virus are unknown. It may have arisen as a hybrid between cowpox virus and variola virus, it may have been derived from cowpox virus or some other orthopoxvirus by serial passage under artificial conditions of culture, or, as Baxby (1981) has suggested, it may be the laboratory survivor of a virus that is now extinct in nature. Whatever its origin, vaccinia virus is clearly a distinct species of *Orthopoxvirus*, and DNA maps of different strains of vaccinia virus are remarkably similar to each other and different from those of all other orthopoxviruses, including cowpox and variola virus (see Chapter 2, Fig. 2.7, 2.9 and 2.10, and Chapter 29, Fig. 29.1). However, like cowpox virus in the hands of Jenner and his followers, it provided inoculated subjects with a high degree of protection against smallpox, with little risk to either the individual or the community.

logical products supply houses of the 20th century.

There was a steady improvement in the quality of the vaccine, the methods for its distribution, and the public health infrastructure, which had reached such a level that by the early 1950s endemic smallpox had been eliminated from the industrialized countries of Europe and North America (see Chapter 8). In the decade after the end of the Second World War, several major advances were made in the production and methods of delivery of the vaccine, but further change and innovation were necessary before global eradication was feasible. This chapter summarizes the state of the art of vaccine production and inoculation, and the results of investigations into the complications of vaccination, as these stood in the period between the end of the Second World War and 1967, when the Intensified Smallpox Eradication Programme was initiated.

During the middle years of the 20th century quarantine measures, which had earlier operated on a national basis in some countries (see Chapter 6), were elaborated and applied on a global scale, with the development of the International Health Regulations by the World Health Organization. The present chapter concludes with an account of the introduction and eventual demise, in 1981, of the International Certificate of Vaccination or Revaccination against Smallpox.

VACCINE PRODUCTION AND QUALITY CONTROL BEFORE 1967

Jennerian vaccination was the tool with which the incidence of smallpox was reduced and the disease eliminated from many countries of Europe and the Americas during the first half of the 20th century. However, at some time during the 19th century, for reasons which are obscure, the nature of the virus used for vaccination changed, in most parts of the world, from cowpox virus to another orthopoxvirus, which came to be known as vaccinia virus.

As scientific virology developed during the 20th century, it was applied to the study of smallpox vaccine and vaccination, and new methods of preparing, distributing and inoculating the vaccine were developed. The descriptions which follow refer to the best methods and procedures in use for vaccine production before 1967. However, because

Vaccine Pulp and Vaccine Lymph

By the end of the 19th century arm-to-arm vaccination had been made illegal in many countries and smallpox vaccine was obtained from animal skin. However, technical knowledge of vaccine production was still extremely poor. For example, even in an advanced industrialized country it was recommended that seed lymph could be obtained from (1) "smallpox direct", (2) cowpox, (3) horsepox, sheep-pox, goatpox, swinepox, or (4) vaccinia in the human body (England and Wales, Ministry of Health, 1928a).

Looked at with modern eyes, the production of smallpox vaccine, even in 1966, was a primitive operation. The method of production, in animal skin, made bacterial contamination inevitable, something that would not have been tolerated in a new viral vaccine in the 1950s.

A number of traditional expressions were used to describe the product obtained at different stages of the process: the animal in which the vaccine was produced was called the *vaccinifer*, the material used for its inoculation the *seed*, the material reaped from the scarified skin the *vaccine pulp*, and the clarified suspension obtained from this the *vaccine lymph*. The pulp was a mixture of epidermal cells and leukocytes, plasma, hair, bacteria and the virus. Clarification removed some of the coarser debris, but the vaccine lymph was milky in appearance on account of contamination with fragments of cells and bacteria. Purified virus, at the concentration found in the lymph, would have been a water-clear suspension.

smallpox vaccine was produced in many countries, in which there were wide differences in the degree of scientific and industrial experience and skill, the procedures employed in some countries were much less satisfactory than those described here. Modifications to traditional production and assay methods, and—most important—the international quality control of vaccines, were introduced shortly after the Intensified Smallpox Eradication Programme began operations in 1967 (see Chapter 11).

Production of Vaccine Lymph

During the first half of the 19th century vaccine was usually made available by arm-to-arm transfer but was sometimes dispatched over long distances dried on threads, ivory tips, or glass slides (see Chapter 6). Cows were first used for the production of vaccine in Italy early in the 19th century; this practice gradually spread around Europe and was universal by the end of the century. Over the years, changes were made in the mode of preparation of both liquid and dried vaccine, but the initial production of vaccine pulp was the same for each.

Choice of vaccinifer

For historical reasons, calves were first used for vaccine production. During the First World War, the Lister Institute of Preventive Medicine, in Elstree, Hertfordshire, England, introduced the use of sheep, a practice subsequently adopted in some other countries. Because of their ready availability, water-buffaloes were sometimes used in India, Indochina and Indonesia, and W. A. Collier (1953) considered them to be superior to other species for vaccine production. Attempts were made in several countries to produce smallpox vaccine in chick embryos and in cultured cells, to avoid the bacterial contamination that was inevitable when production was carried out by scarification of the skin of large animals. However, chick embryo vaccines were produced on a commercial scale only in Brazil, Sweden and the state of Texas in the USA, and only in Brazil were they in widespread use in an eradication campaign (see Chapter 12). Except on a very limited scale, tissue culture vaccines were never produced commercially.

During the 1920s the concept was developed that biological products prepared for use in man should be bacteriologically sterile. Legislation was introduced in some of the industrialized countries to regulate the production of vaccines and similar products. At that time smallpox vaccine grown on the flank of calves was already in wide use. Inevitably, it contained some bacteria, but there was no other practicable method of production. Thus smallpox vaccine was the

Plate 7.1. The preparation of smallpox vaccine at the Vaccine Production Institute, Dhaka, Bangladesh. **A:** Calves to be used for vaccination were held in quarantine for 7 days. **B:** Four days after scarification, the skin was scraped with a sharpened stainless-steel spoon and the vaccine pulp collected in a jar, for subsequent grinding and centrifugation to yield the vaccine lymph.

only vaccine for which both the public and the health authorities accepted the fact of contamination by exogenous microorganisms. Since bacterial contamination was inevitable, the aim in preparing vaccine lymph was to exclude pathogenic bacteria completely and reduce the level of contamination with the normal skin bacteria of the vaccinifer. Choice of a healthy vaccinifer was clearly of major importance. The requisite veterinary inspection was practised in some countries, but in others animals were bought in the market, or even rented to be returned afterwards to their owners. This last procedure circumvented one of the important precautions recommended by producers in developed countries—namely, that a thorough postmortem examination should be conducted when the animal was killed at the end of the incubation period and the pulp discarded if serious disease was found.

Under optimum conditions, every animal used for vaccine production was subjected to an examination by a veterinarian to ensure that it was free from tuberculosis, skin infection and ectoparasites. Only animals which had been free of fever and any sign of disease for at least 2 weeks were used, and during this observation period the animals were clipped and washed.

Preparation of the vaccinifer

The proper preparation of the skin of the vaccinifer was one of the most important steps in obtaining a vaccine of low bacterial content. After being anaesthetized or tranquillized, the animals were washed on an area on the flank or belly, preferably one not liable to soiling by excretions, and then shaved extensively enough to permit a reasonably large area to be scarified. Some producers treated the skin with an efficient skin disinfectant, such as a quaternary ammonium compound, and before vaccination the prepared area was well rinsed with sterile distilled water.

Scarification

The skin was prepared for vaccination by scarification, using the same principle as for the vaccination of humans (see below)—namely, to bring the virus into contact with cells in the Malpighian layer of the epidermis. However, the operation was on a much larger scale, the aim being to produce a confluent take on a large area of the flank and abdomen. The usual procedure was to make a series of parallel scratches about 1 cm apart on the cleansed flank and abdomen of the vaccinifer,

followed by a similar series of scratches at right angles to the first. A wide variety of instruments was used in different laboratories, sufficient force being exerted to produce obvious erythema of the skin, but not bleeding. The prepared skin was then inoculated by rubbing seed virus of high infectivity into the superficial scarifications. Practical considerations limited the extent of the area scarified, because in some countries animals in rather poor health were used, and too extensive scarification might have caused their death.

Two important features which were subject to a great deal of variation in different countries, and sometimes even among different producers in the same country, were the choice of the strain of vaccinia virus and the mode of preparation and maintenance of the seed virus (see below).

Incubation period

Methods of maintaining the vaccinifer until the lesions were ready for harvest differed considerably. Ideally, the scarified area was loosely covered with a cotton cloth, which was changed at least once each day. In the better laboratories, the pen in which the animal was housed was so constructed that the vaccinated animal could not lie down. It had walls that could be washed frequently and a hard floor on which was placed a slatted wooden platform the length of the animal and sloping gently from front to back; the pen was cleaned thoroughly and often. In some countries, however, the vaccinifers were housed in ordinary stables and sometimes they were even turned out to pasture.

The pulp was harvested before crusts formed on the vaccinated area, at a time when both the viral titre and the quantity of pulp were at their maximum. Workers at the Lister Institute found in the 1920s that the viral yield was about the same on the 4th and 5th days after inoculation, but preferred the 4-day incubation period because the opportunity for bacterial contamination and hair growth was reduced by a day.

Harvest

The skin was rinsed with warm water, with or without soap, and the pulp was scraped from the skin with a curette, one form of which was made by sharpening the edge of a hemispherical stainless-steel spoon (Plate 7.1 B). If the animals were killed, exsanguination before scraping ensured a less blood-stained product; if they were not killed, they were usually anaesthetized before scraping. Harvests from individual animals were kept separately in sterile containers closed tightly enough to prevent drying by evaporation, and stored below 0 °C except when being processed.

Seed virus used for inoculation

The seed viruses used in various laboratories differed with regard to the strain of virus employed and the titre of the inoculum, as well as the methods by which they were maintained.

Strain of vaccinia virus. With a procedure that had been in use in many countries for over a hundred years, and with no effort at international standardization, it was not surprising that the strains of virus employed for vaccination in different countries differed in their biological properties. The choice of a particular strain was arbitrary, being based on the history of the vaccine production laboratory concerned. An examination of the situation in 1967 showed that many different strains were then in use (see Chapter 11). This can be understood when it is realized that during the 19th century vaccine production was an unregulated activity, undertaken by a large number of "backyard" producers. For example, as A. C. Hekker has commented (personal communication, 1981), in 1875 there were about 15 *"parcs vaccinogènes"* in a country as small as the Netherlands, with at least 1 in every province. By 1900 the number had been reduced to 3—in Amsterdam, Groningen and Rotterdam respectively. Finally, in 1954, production was centralized in the National Institute of Public Health, Bilthoven. The situation was similar in many other countries—for example, in Great Britain, where lymph maintained by arm-to-arm inoculation was used until the 1890s.

Since different strains of vaccinia virus vary considerably in their biological properties (see Chapter 2) and since the properties of the viral strain were probably important in determining the differences found in the rates of occurrence of postvaccinial encephalitis in different countries (see Table 7.8), this was not a trivial matter. However, no steps were taken to recommend internationally which vaccinia strain should be used for vaccine production until after 1967 (see Chapter 11), although some countries in which postvac-

The Stability of Vaccinia Virus

Stocks of all viruses, even after cloning (i.e., being grown from a single plaque or pock and thus a single viral particle), contain a small proportion of mutant virions (see Chapter 2). Most attenuated live virus vaccines were developed by selecting for certain of these mutants by continued serial passage of concentrated viral suspensions in a novel host. With an agent that was suitable to start with, such as vaccinia virus, the reverse sometimes occurred. The early vaccinators believed that serial passage in humans "weakened" the vaccine, and they resorted to periodic "retrovaccination"—i.e., passage of the virus in cows—to enhance its potency (see Chapter 6). Subsequently, some manufacturers observed that continued serial passage in calves led eventually to a fall in the take rates of the vaccine in man, although others (e.g., W. A. Collier, 1953) found that potency was maintained throughout 35 serial passages in water-buffaloes.

Manufacturers sought to overcome the fluctuations in potency by periodic passage of the seed virus in other animals, usually the rabbit but sometimes monkeys, donkeys or even human subjects. These manipulations were rendered unnecessary by the development of the "seed lot" system.

cinial encephalitis had been a serious problem had changed their production to the less pathogenic Lister strain before this.

Titre of inoculum. All authorities agreed that it was desirable to use an inoculum with as high a titre as possible. Two methods for measuring the titre had been used after the Second World War: scarification of the skin of a rabbit and pock counts on the chorioallantoic membrane of the chick embryo. The rabbit-skin assay, which consisted of a series of scarifications of 10-fold or sometimes 3-fold dilutions of the material under test, was not very precise, hence many producers could not make accurate estimates of the titre of either their inoculum or their product. Pock counting, although early shown to be very suitable for the assay of vaccinia virus (Keogh, 1936), did not come to be widely used by vaccine producers until the 1950s.

Maintenance of seed virus. As recently as 1966, many manufacturers still used some of the vaccine lymph prepared for distribution as the inoculum for the next series of vaccinifers, a procedure that over the years involved a large but unknown number of serial passages of the virus in these animals. Other manufacturers passed the virus in the skin of man or the rabbit after a certain number of subcultures in calves, or alternately in vaccinifer and rabbit. Meeting in 1958, a WHO Study Group on Requirements for Smallpox Vaccine (1959) recommended the use of the seed lot system. This involved, in principle, laboratory maintenance at refrigerator temperature of large stocks of a primary seed lot of a suitable preparation of vaccinia virus. From this primary seed lot enough virus had to be prepared for the production run. Depending on its titre, the extent to which it multiplied and the number of vaccinifers used, the primary seed was passaged once or several times by the scarification of single calves to obtain the seed lot for the production run. The number of such serial passages of the virus in the vaccinifer was usually restricted to 5. With this method, possible alteration of the strain could be limited, the chance of extraneous contamination was reduced, and the inoculum could be standardized in terms of viral concentration and freedom from contamination.

Preparation of Liquid Vaccine

Traditionally, the vaccine pulp was processed so as to remove some of the extraneous material and reduce the bacterial count, and it was then dispersed as a liquid suspension called vaccine lymph.

Clarification of the vaccine pulp

The semisolid pulp was usually ground into lymph by comminuting it in a grinder, or later by homogenization in a blending machine. For this purpose it was usually mixed with 40–60% glycerol. Storage of the glycerolated homogenate at low temperature over a period of months led to a steady fall in the number of viable bacteria, but it was later

found that the same result could be more rapidly achieved by the addition of phenol (see below). Periodically bacteriological tests were made to determine when the lymph was suitable for distribution.

Use of glycerol

The introduction of glycerol to "stabilize" the vaccine virus and at the same time prevent bacterial multiplication was regarded as a major step forward in lymph production. This procedure made it feasible to change from arm-to-arm vaccination or the use of an itinerant vaccinated cow (see Chapter 6, Plate 6.12) to the distribution of liquid vaccine in capillary tubes.

Glycerol had three advantages: it acted as an antibacterial preservative, it helped to make the vaccine stick to the skin, and it permitted the maintenance of the vaccine in liquid form at −10 °C and thereby ensured the long survival of active vaccinia virus. It also prevented ice formation, a process which, in the presence of phenol (contained in nearly all smallpox vaccines), led to the reduction of viral infectivity.

However, although Copeman (1892, 1899) had claimed that glycerol was bactericidal but not virucidal, subsequent work showed that at temperatures above 0 °C it inactivated vaccinia virus rather rapidly. The deleterious effect of glycerol was of little importance in countries with temperate climates, especially if good refrigeration was available, but it was an important cause of vaccine failure in tropical areas.

Use of phenol

The bacterial count in glycerolated pulp stored in the refrigerator fell off very slowly. Several months were usually required before it was low enough to allow the vaccine to be issued for use, and repeated testing was necessary during this period. The procedure could be greatly accelerated by adding phenol to a final concentration of 0.5%, a procedure originally recommended by Gins (1924) and Lehmann (1937) and popularized by McClean (1949), whose protocol was as follows: Material harvested from the sheep was ground with twice its weight of a 1% solution of phenol in distilled water. After this had stood at 22 °C for 48 hours, glycerol, equal in amount to the phenol solution, was added, so that the final concentration of phenol was 0.4%.

Mode of distribution

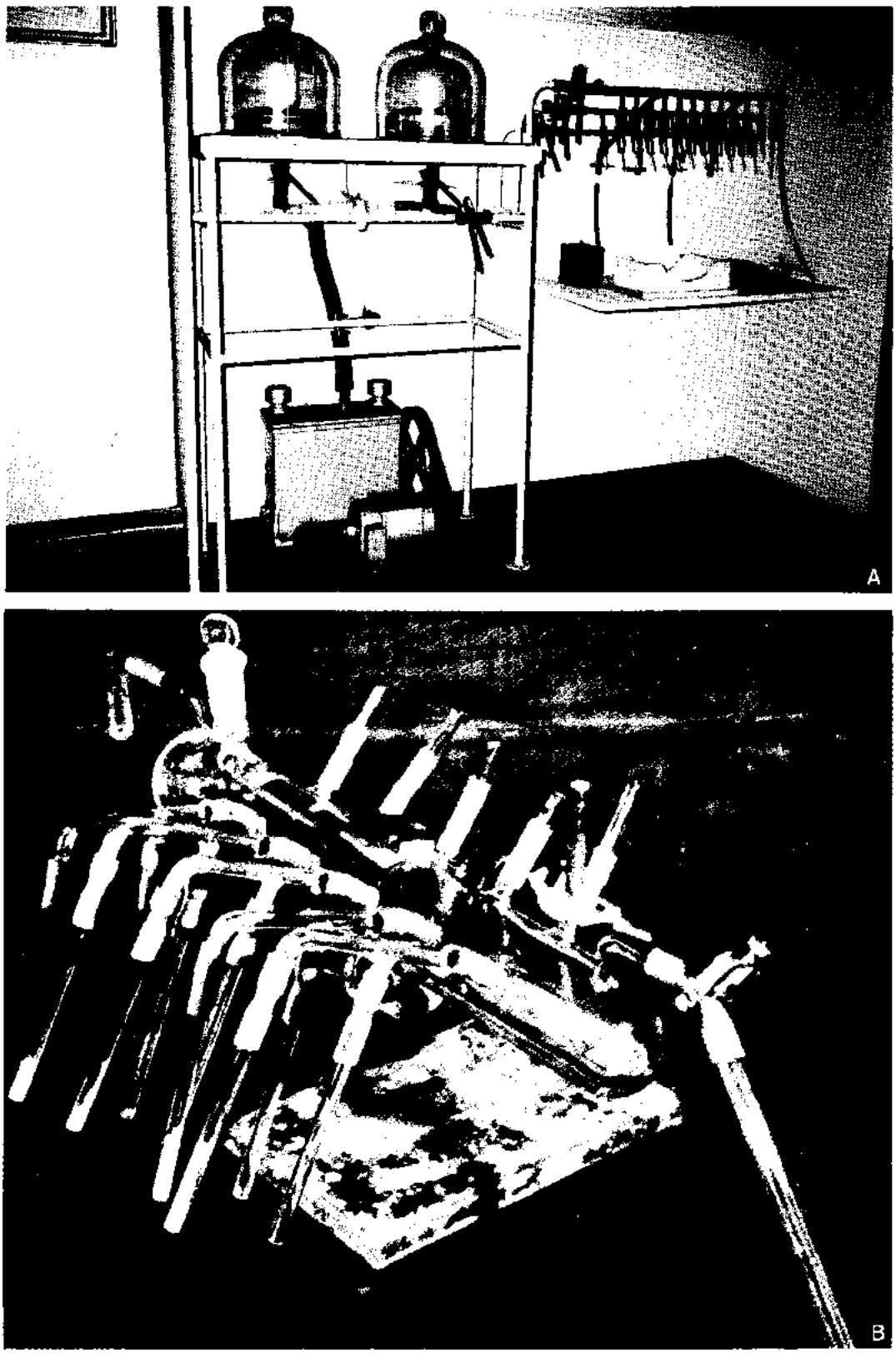
Liquid vaccine was usually dispensed in glass or, later, plastic capillary tubes, in single-dose lots or in amounts sufficient for about 20 vaccinations.

Preparation of Dried Vaccine

Liquid vaccine was satisfactory in temperate countries with well-developed health services, good transportation networks and reliable refrigerator capacity. Endemic smallpox was eliminated from Europe and North America by vaccination with liquid glycerolated vaccine, even though its potency was sometimes lower than desirable. At this time many authorities favoured the use of multiple sites of insertion (usually 2 or 4), a procedure which continued up to the 1960s in India and which sometimes produced a satisfactory take even with a substandard vaccine. However, liquid vaccine was totally unsatisfactory for tropical countries, as reports from medical officers in those areas attested. In 1919, for example, the complaint was made in Africa that even for primary vaccination "only 7–20% positive results were obtained with the best vaccine" (Tanganyika Territory, 1920). Likewise, in Madras, Hobday et al. (1961) obtained a 27% take rate in revaccinations with fresh liquid vaccine compared with a 63% take rate with freeze-dried vaccine. Because of its low heat stability, health authorities sometimes went to great trouble to try to maintain the potency of liquid vaccine. In Peru, for example, in the period before freeze-dried preparations became available, vaccine was carried in the field in kerosene refrigerators mounted on the backs of mules (C. Quirós, personal communication, 1984).

Air-dried vaccines

It was recognized very early that dried vaccine often survived far longer than liquid vaccine when both were maintained at ambient temperatures, and Jenner himself distributed vaccine dried on threads or between glass slides. Over the years a variety of methods for drying liquid vaccine were employed (L. H. Collier, 1954). Among the more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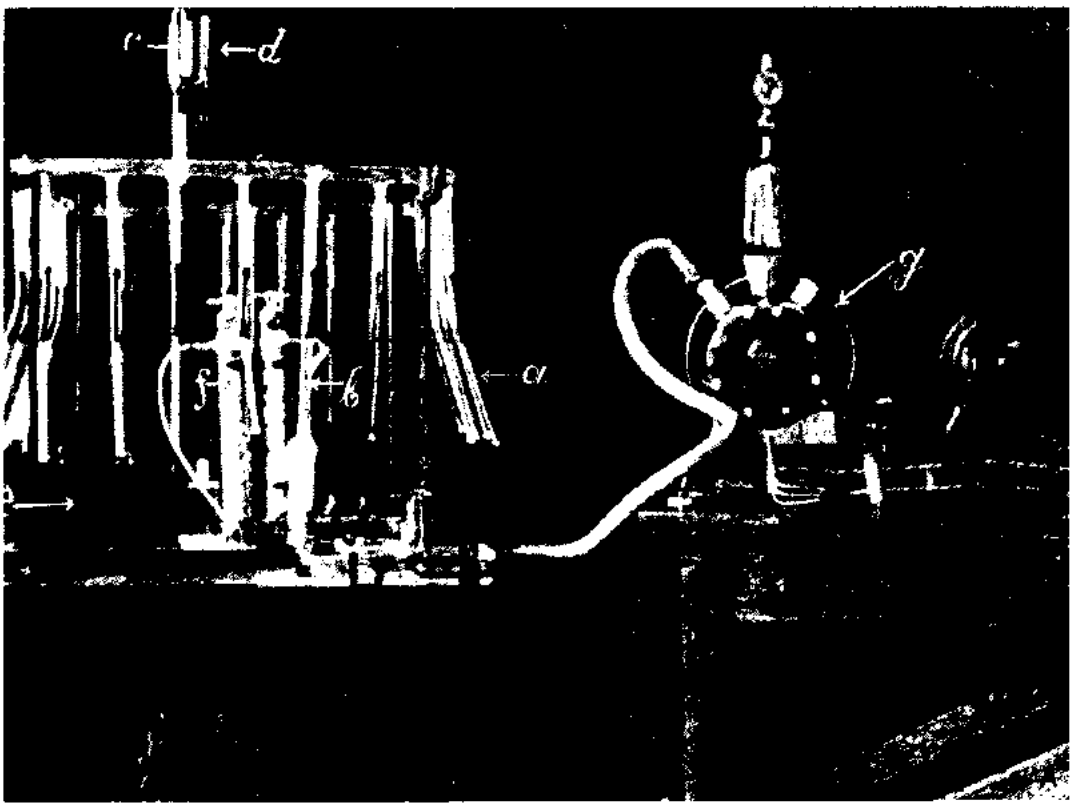


Plate 7.2 (*facing page*). **A:** Apparatus developed by Camus and Fasquelle and used for the preparation of freeze-dried vaccine from 1917 onwards. **B:** Apparatus developed by Hornibrook (1949) for preparing freeze-dried vaccine. (From Hornibrook, 1949.)

BY COURTESY OF C. QUIROS

Plate 7.3 (*above and right*). **A:** Apparatus used by Otten (1927) for evacuating ampoules containing air-dried vaccine before sealing. (From Olivier et al., 1932.) **B:** Commercial development of Hornibrook's apparatus used for making freeze-dried vaccine in Peru in the early 1950s.

effective were those devised by Camus (1909), working at the Vaccine Institute in Paris and concerned to produce an effective vaccine for use in French colonies in the tropics, and by Otten (1927), working in Batavia (Jakarta). Camus placed vaccine pulp in a thin layer under an evacuated bell jar, in the presence of sulfuric acid. The pulp was cooled and shaded from light, and drying was complete within a few hours. In tests in western Africa, after transport at ambient temperatures, it gave take rates in different trials of 66–100%. Otten used a similar procedure: buffalo lymph was dried *in vacuo* over sulfuric acid, at room temperature. Subsequently the ampoules were attached to a manifold and sealed under vacuum (Plate 7.3A). Although the results were variable, the majority (80%) of preparations of such dried vaccine produced takes in 75–100% of primary vaccinees, after storage at room temperature in Batavia for 16–30 months or at 37 °C for 12 months (Otten, 1932; W. A. Collier, 1953).

Otten's vaccine was an important factor in achieving the elimination of smallpox from the Netherlands East Indies (now Indonesia) in 1937 (see Chapters 8 and 13). However, there was considerable batch-to-batch variation, the vaccine was often heavily contaminated with bacteria, and it was difficult to reconstitute. Further, the technique did not lend itself readily to large-scale production.

Freeze-dried vaccines

In 1909 Shackell reported an improved method of drying biological materials, based on the fact that H_2O could pass directly from a solid to a gaseous state. He deep-froze the biological material and sublimated it *in vacuo*. During the First World War, Wurtz & Camus (1919) produced a freeze-dried vaccine which was packed in tubes under vacuum. Samples prepared by this method were active after several weeks at 37 °C and, when transported from France to Côte d'Ivoire, Guinea and French Guiana, gave take rates of 85–100% (Fasquelle & Fasquelle, 1949) (Plate 7.2A).

Approximately 10 million doses of this dried vaccine were sent every year between 1920 and 1940 to the French colonies in Africa for the smallpox vaccination campaign, and the Vaccine Institute in Paris continued to supply it to the francophone countries of Africa until 1966, in amounts ranging from 4 to 12 million doses annually (J. Fasquelle, personal communication, 1983). During the eradication programme in western Africa in 1967 (see Chapter 17), it was found that smallpox was less of a problem in countries that had been French colonies, in part because of their previous use of freeze-dried vaccine.

Meanwhile, from the 1930s onwards various laboratory workers in other countries had adopted freeze-drying for the preservation of vaccinia virus (Rivers & Ward, 1933, 1935; Lloyd & Mahaffy, 1935; Hahn, 1951; L. H. Collier, 1951). The technology was substantially improved by Flosdorf & Mudd (1938). A freeze-dried vaccine developed by Kaiser (1937, 1942) was said to have been used extensively by the German army during the Second World War (cited by L. H. Collier, 1954).

In 1948, the year in which the World Health Organization was established, a WHO study group on smallpox vaccine met in Paris and reported to the First World Health Assembly that freeze-dried vaccine such as that prepared at the Paris Vaccine Institute (using the method developed by Wurtz & Camus) had proved to be an effective heat-stable vaccine in the French colonies for a number of years. Stimulated by these reports, Dr Fred L. Soper, then Director of the Pan American Sanitary Bureau, encouraged the United States National Institutes of Health to carry out studies on appropriate methods for the production of freeze-dried smallpox vaccine, in order to fulfil the proposal made by the Executive Committee of the Pan American Sanitary Organization in 1949 that all countries in the Americas should cooperate in national programmes designed to eradicate smallpox (Soper, 1966). The technical investigations were undertaken by the Division of Laboratories, Michigan Department of Health, then a leading producer of glycerolated liquid vaccines (Ducor, 1947). They resulted in the development of a method for freeze-drying vaccine that had been dispensed in 0.5-ml lots in Pyrex tubes (Hornibrook & Gebhard, 1951), using a sulfuric-acid drier (Plate 7.2B) developed by Hornibrook (1949). Peru was the first country in the Americas to use this process on a commercial scale, beginning in October 1953.

In June 1952, WHO organized comparative studies on the heat stability of freeze-dried vaccine produced by the Vaccine Institute, Paris, the State Serum Institute, Vienna, the Division of Laboratories, Michigan Department of Health, Lansing, USA, and the

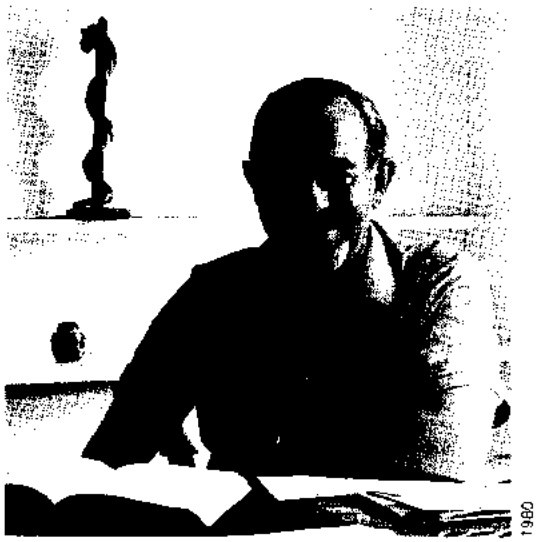


Plate 7.4. Leslie H. Collier (b. 1921). As a graduate student at the Lister Institute of Preventive Medicine, Elstree, Herts., England, in the early 1950s Dr Collier developed the method of freeze-drying of vaccinia virus that was subsequently adapted to large-scale freeze-dried vaccine production in many laboratories throughout the world.

Pasteur Institute, Bandung, Indonesia. The tests were carried out in the State Serum Institute, Copenhagen, the Division of Laboratories, Michigan Department of Health, the Vaccine Institute, Paris, the Lister Institute of Preventive Medicine, Elstree, and the New York City Department of Health. No laboratory performed the tests on vaccine that it had itself produced. The results showed that the heat stability of the vaccine provided by the Michigan Department of Health was the best of the 4 tested.

The large demand for human plasma proteins for use in the Second World War had led to further advances in the technology of freeze-drying, notably the introduction of a centrifugal freeze-drying apparatus (Greaves, 1946). L. H. Collier (1951), working at the Lister Institute as a graduate student under the direction of D. McClean, applied this technique, with the addition of peptone as a stabilizing agent, to the preservation of vaccinia virus and subsequently developed it for large-scale commercial production (L. H. Collier, 1955). WHO decided to conduct an additional test to compare the new Lister Institute vaccine with the freeze-dried vaccine from Michigan. Samples maintained at 37 °C and 45 °C for various periods were titrated by pock counting on the chorioallantoic membrane and by scarification in rabbits and tested by primary vaccination of Royal Air Force personnel (Cockburn et al., 1957). The Lister freeze-dried vaccine was found to give 100% successful takes after storage for 64 weeks at either 37 °C or 45 °C. The Michigan vaccine was much less heat stable, the take rate falling to 72% after 16 weeks and 10% after 32 weeks at 37 °C (Table 7.1), and to 47% after 4 weeks at 45 °C. The results of titration of the two vaccines by pock counting on the chorioallantoic membrane, in an independent laboratoty, were consistent with these results, in that the Lister vaccine maintained its titre whereas that of the Michigan vaccine fell off steadily after storage.

As further modified by C. Kaplan, by the substitution of fluorocarbon treatment for differential centrifugation as a method of partial purification, L. H. Collier's method was eventually adopted by WHO for the global smallpox eradication programme (see Chapter 11).

Subsequently, freeze-drying technology was greatly improved for the large-scale commercial production of vaccine, particularly in the methods of filling and sealing ampoules. The availability of a method for the long-term preservation of vaccine in tropical climates was an important factor in encouraging countries to participate actively in the global smallpox eradication programme.

Vaccine pulp destined for freeze-drying was prepared as for liquid vaccine, except that glycerol was not added. In some laboratories it was diluted or concentrated according to its potency on assay. In order to reduce bacterial contamination to an acceptable level, phenol was added to the bulk solution of the vaccine so that its final concentration did not exceed 0.5%.

Before 1967, the bulk solution was put into special ampoules or vials containing 0.25, 1.0 and 5.0 ml, corresponding respectively to 25, 100 and 500 doses. These were then placed in a freeze-drier, of which there were two types: the centrifugal drier and the shelf drier (see Chapter 11, Plate 11.7). The former required the use of a secondary drier, which consisted of a number of manifolds mounted over phosphorus pentoxide as a desiccant, while the latter provided both primary and secondary drying and sealing of the containers under vacuum inside the drier.

Development of Freeze-dried Smallpox Vaccine

"In 1948, I was told by the then Director [of the Lister Institute], Dr (later Sir) Alan Drury, that there was a great need for a smallpox vaccine that would be stable at tropical temperatures. He asked if I would be interested in this problem, and suggested that freeze-drying—in which he himself was concerned as a means of preserving blood plasma—might be a useful technique.

"At the outset I aimed for a method that would yield consistent heat stability results and set myself these additional criteria: the vaccine must still comply with the official standard of potency after at least one month at 37 °C (a requirement later adopted by the British and European Pharmacopoeias and by WHO); if dried, it must be safe and easy to reconstitute in the field by vaccinators with little technical training; and it must be possible to produce it economically on a large scale. In addition, it would of course have to comply with the official regulations on bacterial contamination.

"In my field experiments I compared the stabilities of the glycerinated and lanolinated vaccines in current production; although the latter was the more stable at 22 °C, it completely lost its potency within a month at 37 °C. I then tried Otten's method of drying crude vaccine from the liquid state over sulphuric acid; vaccine made in this way was widely used in Indonesia and some batches had survived at ambient temperatures for remarkably long periods. There was however considerable batch-to-batch variation, a finding that I confirmed; furthermore, the bulk dried vaccine was cumbersome to handle and distribute into ampoules.

"Without further ado I then started to explore the possibilities of drying from the frozen state, using a large centrifugal dryer of the type that had recently been invented by R. Greaves at Cambridge. This machine was made in the Institute's workshops and although primitive in appearance, it worked very well; the main difficulty was the making of vacuum-tight seals, at that time rather more of an art than a science.

"The general plan was to prepare experimental vaccines in various ways, to freeze-dry part of the batch and then to compare the keeping properties of the dried and corresponding liquid preparations at 4 °C, 22 °C and 37 °C. Each batch was tested monthly, sometimes for more than two years. It was soon clear that dried lots of routinely-produced animal skin vaccine varied considerably in stability; materials partly purified by differential centrifugation yielded much more uniform results.

"The next problem was rather more difficult. Phenol was added to destroy contaminating bacteria; this had to be done before drying, otherwise the bacteria would have been preserved along with the virus. Although phenol in low concentration does not harm vaccinia virus in liquid suspensions, vaccines containing it lost much of their potency on freeze-drying; this was eventually traced to the tendency of phenol to come out of solution during rapid cooling and become concentrated to a degree that killed the vaccinia virus. This effect could however be prevented by adding peptone to a concentration of 5% before drying the vaccine. Fortunately, among the many additives tried, peptone also proved by far the best for preserving potency at all temperatures tested; it had the further advantages of being non-antigenic, cheap and easy to reconstitute.

"After much experimentation, a satisfactory method was devised for purifying animal vaccine and freeze-drying it after adding peptone to a concentration of 5%. Vaccine thus prepared consistently maintained its original potency for at least three months at 37 °C; in later experiments, batches stored at the high temperature of 45 °C still gave 100% successful primary vaccination after four years. The criterion for the permissible minimum content of vaccinia virus was fixed by determining the amount of virus needed to achieve 100% successful vaccinations; the final step in the development stage was the devising of a simple and safe method for reconstituting the dried vaccine in the field. It then remained only to scale up all the processes to a point at which full production could begin; this was accomplished by 1953." (L. H. Collier, personal communication, 1980.)

Table 7.1. Relation between potency measurements of preparations of freeze-dried vaccine (Michigan) stored at 37 °C for various periods, by pock counting on the chorioallantoic (CA) membrane and by rabbit-skin scarification[a,b]

Storage conditions	Testing laboratory	CA membrane titre (pock-forming units per ml)	Rabbit scarification titre						Primary vaccination success rate (%)
			1:10	1:100	1:1 000	1:3 000	1:9 000	1:27 000	
−10 °C	A	1.5×10^7	–	–	c	c	sc^+	6	100
	B	2.9×10^6	–	–	c	c	c	8	
4 weeks at 37 °C	A	3.4×10^7	–	c	sc^+	sc^-	6	1	96
			–	c	c	6	1	3	
	B	1.5×10^6	–	–	6	0	0	0	
			–	–	4	0	0	0	
8 weeks at 37 °C	A	3.6×10^6	c	c	c	sc	5	0	96
			c	sc^+	5	0	0	0	
	B	8.5×10^5	–	c	6	1	0	–	
			–	sc	6	4	3	–	
16 weeks at 37 °C	A	4.8×10^5	c	sc	6	0	0	–	72
			c	sc^+	2	2	0	–	
	B	10.3×10^5	–	c	c	1	0	–	
			–	sc	sc	1	0	–	
32 weeks at 37 °C	A	5.1×10^4	3	0	0	0	–	–	10
			?	0	0	0	–	–	
	B	10.2×10^4	4	1	0	–	–	–	
			5	0	0	–	–	–	

[a] From Cockburn et al. (1957).
[b] KEY:
– = no test.
c = confluent lesion, 100% of the area.
sc^+ = semiconfluent lesion, 70–80% of the area.
sc = semiconfluent lesion, 50–70% of the area.
sc^- = semiconfluent lesion, less than 50% of the area.
Figures shown under "Rabbit scarification titre" indicate number of discrete vesicles.
A = Lister Institute of Preventive Medicine.
B = Department of Bacteriology, University of Liverpool.

Quality Control

At the national level

Smallpox vaccine had been used for many years before the concept developed that it should be subject to national quality control, in addition to whatever steps the manufacturer might take to protect the reputation of his products. By the mid-1920s a few countries had developed regulations governing biological products destined for medical use, such as vaccines, toxoids and sera.

In January 1926 the Smallpox and Vaccination Commission of the Health Organisation of the League of Nations decided to collect information from vaccine producers regarding the production, testing, standardization, storage and delivery of smallpox vaccine. France, Germany, the Netherlands, Switzerland and the United Kingdom participated in this survey, which was completed in 1927. On the basis of the results, the United Kingdom incorporated standards into the Therapeutic Substances Regulations 1927 (England and Wales, Ministry of Health, 1928a). A brief review of these regulations provides some information on how the quality control of smallpox vaccine was then being conducted in the United Kingdom. The regulations defined certain conditions concerning the qualifications of staff, the animals to be used, the housing of such animals, precautions to be observed during the production process, specifications for final containers for the use of the vaccine, and labelling. The provisions relating to the purity of the vaccine indicated that each batch should be tested to ensure the absence of anaerobic organisms and streptococci: bacterial counts should be less than 5000 per ml. Scarification of the cornea of guinea-pigs or the skin of rabbits with diluted vaccine lymph was the principal method for potency testing, typical vaccinia lesions being regarded as the criterion for adequate potency. It seems likely that the quality control of vaccine lymph was being carried out along these lines in many other

countries of Europe and perhaps in North America at that time. During this period the application of the control system depended on the interest and capabilities of the production laboratory, since there was no mechanism for independent assessment.

At the international level

In 1946 the Interim Commission of the World Health Organization was set up, taking over the functions of the Health Organisation of the League of Nations. The Commission established a section (unit) of Biological Standardization in the Secretariat. The responsibilities of this section included the establishment of international standards for biological assay, the formulation of requirements for biological products, the coordination of research on biological standardization and the encouragement of Member States to set up national control laboratories for biological substances (Outschoorn, 1973).

WHO standards for smallpox vaccine were first established in 1958, at a meeting in which 6 experts from Europe, 2 from North America, 2 from Asia, and 1 from North Africa participated (WHO Study Group on Requirements for Smallpox Vaccine, 1959). This meeting suggested the criteria that should be established for smallpox vaccine, in relation to the strain of vaccine, methods of preparation of the vaccine lymph, bacterial counts, use of the seed lot system, methods of potency assay and standards for the heat stability of freeze-dried vaccine. In 1965 these requirements were revised in the light of experience accumulated during the intervening period (WHO Expert Group on Requirements for Biological Substances, 1966). Meanwhile, after extensive collaborative studies, the first reference preparations of smallpox vaccine were established in 1962 (ampoules containing 14 mg of freeze-dried smallpox vaccine; Krag & Bentzon, 1963) and of anti-smallpox serum in 1965 (ampoules containing 84.3 mg of freeze-dried pooled human serum—1000 IU per ampoule; WHO Expert Committee on Biological Standardization, 1967). These reference preparations were produced with a view to facilitating the laboratory investigations needed in order to improve vaccine quality. The modifications proposed in 1965 reflect the progressive improvement in vaccine production and assay.

Seed lot system. In the 1959 WHO requirements, up to 10 serial passages of the seed virus were permitted. Meanwhile, advances in viral genetics and practical experience with poliovirus vaccine had drawn attention to the need to minimize the serial passage of seed virus if genetic stability was to be maintained. In response to this new knowledge, the acceptable maximum number of passages of vaccinia virus secondary seed lots was reduced to 5.

Bacterial count. In 1959 the acceptable count was set at less than 1000 non-pathogenic bacteria per ml, whereas in 1965 this number was reduced to less than 500 per ml, because manufacturers had improved their techniques for the handling of animals and the collection of the vaccine pulp.

Potency. Cockburn et al. (1957) found that vaccine with a titre of 1.5×10^7 pock-forming units per ml gave 100% successful takes in groups of about 100 primary vaccinees, and in a more elaborate statistical analysis of their data (published as an annex to the article cited), C. C. Spicer showed that vaccines with a potency of 10^8 pock-forming units per ml should give less than 1 failure in 1000 primary vaccinations. In 1959 a titre of 5×10^7 pock-forming units had been recommended as the minimal acceptable potency, but in 1965 the level was doubled, to 10^8 pock-forming units per ml. This change was based on observations made by the WHO Expert Committee on Smallpox (1964), to the effect that:

> "... vaccines of relatively poor potency are adequate for successful primary vaccination but inadequate for successful revaccination. Their use for revaccination gives a false sense of security, since a negative response is often taken as evidence of immunity. Failure in successful revaccination explains in part the continued presence of smallpox in some endemic countries where vaccination is regularly practised."

Changes were also made in the recommended method of titration. Following the observations by Cockburn et al. (1957) that pock counting was considerably more precise than rabbit scarification (see Table 7.1) and that pock counts correlated well with take rates (Fig. 7.1), the 1959 recommendation that rabbit-skin scarification and pock counting were acceptable alternatives was changed so as to eliminate scarification.

Heat stability. The requirements for heat stability remained unchanged; vaccine

should maintain the minimum acceptable potency (now 10^8 pock-forming units per ml) after incubation at 37 °C for 4 weeks.

Implementation of the WHO recommendations. The WHO requirements for smallpox vaccine established in 1965 remained in effect throughout the Intensified Smallpox Eradication Programme. However, the promulgation of standards by WHO in 1959, and again in 1965, and their application in laboratories in diverse countries were very different matters, especially before the WHO Smallpox Eradication unit organized an international quality control system in 1968. Before that, many laboratories lacked competent staff, adequate facilities and interest. Some production laboratories did no potency assays at all; others relied on tests in unvaccinated children, regarding 9 takes out of 10 as satisfactory (a result that could be obtained with a vaccine whose titre was as low as $10^{6.5}$ pock-forming units per ml; see Fig. 7.1). For producers who did wish to titrate their production lots, reference preparations of known titre were required. However, only 2 or 3 ampoules of the international reference vaccine, prepared in 1962, were supplied to production laboratories, from which the laboratories were expected to produce their own working standards. In developed countries this was no problem, but it was beyond the capacity of many laboratories in developing countries. Further, some developed countries did not adopt the standards recommended by WHO. For instance, in the USA, the rabbit-skin scarification method was still used as the method for estimating the potency of smallpox vaccine until 1971. In Japan, a titre of 5×10^7 pock-forming units per ml remained the officially accepted minimum level of potency for several years after 1965. National quality control of smallpox vaccines was exercised in only a few countries.

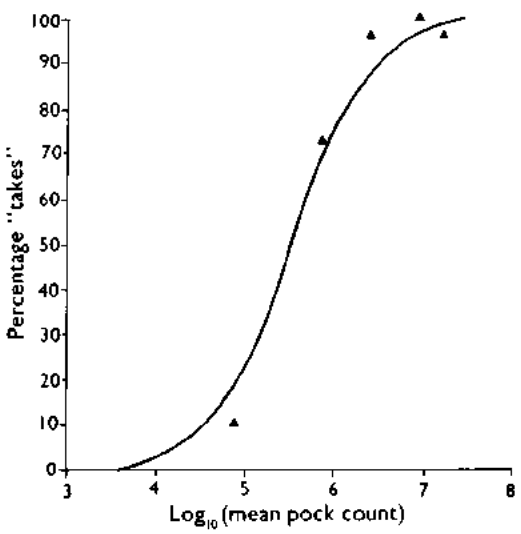


Fig. 7.1. Relationship between pock counts of vaccinia virus and the percentage of successful takes on primary vaccination. The solid line represents a theoretical curve based on probit analysis assuming a 50% probability of a take at a dose of 3×10^5 pock-forming units per ml. (From Cockburn et al., 1957.)

From 1959 to 1966, WHO's participation in monitoring the quality of vaccine was limited to material which had been donated to the Organization for use in the global eradication programme. This amounted to only about 7 million doses a year (total over the period: some 46 million doses; see Chapter 11, Table 11.1). Material supplied through bilateral assistance or by local production was not tested by WHO. This often resulted in the use of substandard vaccine. As A. S. Outschoorn, former Chief Medical Officer of the WHO Biological Standardization unit, said:

> "It has never been feasible for W.H.O. laboratories to be established which would undertake control of biological products on behalf of Member States. There would perhaps be a place in the future for private enterprise to make available sources of expertise or advisory services and even testing facilities from which Member Governments could call for assistance outside of the World Health Organization." (Outschoorn, 1973.)

The absence of effective quality control was one of the first obstacles that had to be overcome when the Intensified Smallpox Eradication Programme was established in 1967 (see Chapter 11).

VACCINATION TECHNIQUES BEFORE 1967

During the long history of vaccination, practices and techniques were gradually developed that differed from country to country. However, by the 1950s they shared many features, which are summarized below.

Vaccination Site

The most commonly used site for primary vaccination and revaccination was on the

"Vaccination" and "Immunization"

The term "vaccination" sometimes causes confusion because it has both a specific and a general meaning. Vaccination against smallpox was the only form of preventive immunization against an infectious disease until 1880, when Pasteur developed techniques of attenuation of virulence and protective inoculation of animals against anthrax and chicken cholera. In 1881, in order to recognize Jenner's contribution to the concept of inoculation with attenuated microbes as a method of protection against infectious diseases, Pasteur proposed that this procedure should be called "vaccination" and the product used a "vaccine", whatever its nature. This terminology remains in use, though the general procedure is now usually called "immunization"; the product is still called a vaccine—e.g., poliovaccine, measles vaccine. In this book "vaccine" always means smallpox vaccine unless specified in some other way.

extensor surface of the upper arm, over the deltoid muscle. In some parts of India, however, revaccination was carried out on the flexor surface of the forearm.

The skin site was usually rubbed with alcohol or acetone. Although studies described in Chapter 11 showed that such skin preparation was unnecessary and could, if the alcohol did not completely evaporate, partially inactivate the vaccine, the practice continued to prevail in many countries.

Methods of Vaccination

Several methods were used, all involving the introduction of the virus into the Malpighian layer of the epidermis, with a variety of instruments (Plate 7.5). In most countries, either the skin was scarified by a single linear incision or scratch, or vaccine was introduced into the epidermis by the multiple pressure method, but in a few places a rotary lancet was used.

Dermal scarification

A scratch about 5 mm long was made in the skin with a needle, a lancet or a small knife and the vaccine suspension was rubbed into the site. A single cut or cross cuts were made, in 1, 2 or 4 different sites. This was essentially the same method as had been used for variolation in Europe during the latter part of the 18th century.

Multiple pressure method

From very early times attempts were made to deposit virus between the skin layers by methods other than the scratch method or intradermal inoculation with a syringe and needle. Leake (1927), in a pamphlet offering official advice on vaccination to physicians in the USA, recommended the "multiple pressure" method (Fig. 7.2), which was subsequently adopted in several other countries (Parish, 1944; England and Wales, Ministry of Health, 1956). A small drop of vaccine was placed on the skin and the side of a straight surgical needle, held tangentially to the skin surface, was pressed firmly and rapidly into the drop by an up-and-down motion, about 10 times for primary vaccination and 30 times for revaccination. Excess vaccine was wiped off. Only 1 insertion site was recommended, for both primary vaccination and revaccination. This method was less traumatic than scarification, while still producing an adequate take. However, it was difficult to train vaccinators to exert sufficient pressure, and this sometimes caused unsuccessful vaccinations.

Rotary lancet

Vaccination using the rotary lancet (Plate 7.5) was carried out in many parts of the Indian subcontinent. A rotary lancet designed for vaccination was first described by Rose (1871) and was manufactured in the United Kingdom and later in India. The vaccine was placed on the skin with the small spoon on one end of the instrument. The disc, anchored by the slightly longer central spike, was rotated in such a way that the small lateral spikes abraded the epidermis. If potent vaccine was used, the ensuing trauma produced a large and severe vaccinial reaction, which was a frequent cause of refusal to undergo vaccina-

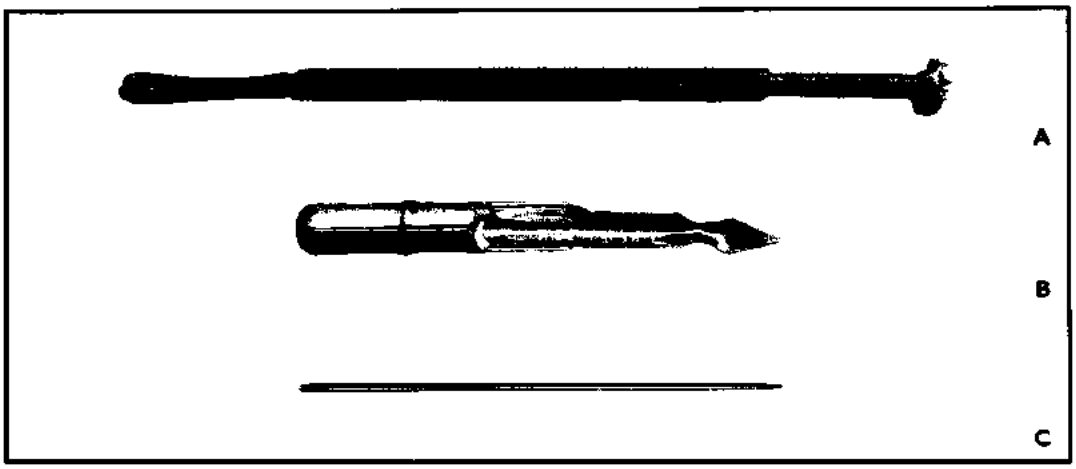


Plate 7.5. Instruments used for vaccination (actual size) before the introduction of the bifurcated needle. **A**: Rotary lancet. **B**: Vaccinostyle, used for scratch vaccination. **C**: Straight surgical needle, used for vaccination by scratch or multiple pressure method (See Fig. 7.2).

tion. Further, the vaccines then in use were often heavily contaminated with bacteria and the use of the rotary lancet could produce scarring even when the infection had been due to pyogenic bacteria rather than vaccinia virus. Failures sometimes occurred when vaccinators did not allow the lancet to cool adequately after the flaming that was carried out after each vaccination.

Although the WHO Expert Committee on Smallpox (1964) recommended that this method should not be used, it was still routinely employed in some parts of the Indian subcontinent long after this. During the smallpox eradication programmes in Pakistan and India (see Chapters 14 and 15), the programme staff hunted for rotary lancets and confiscated a large number of them from vaccinators who were reluctant to abandon the method but were thus obliged to use the bifurcated needle. However, many remained in use, particularly in the municipal corporations in India, as late as 1974.

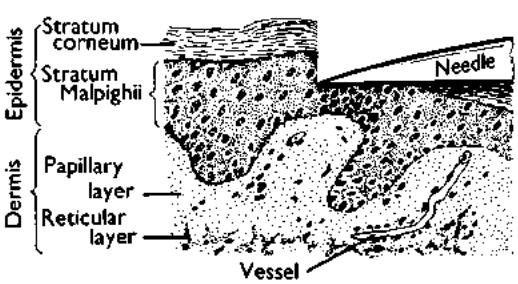


Fig. 7.2. The principle of the multiple pressure method of vaccination. Virus on the tip of the needle is deposited within the deeper layers of the epidermis.

Age for Primary Vaccination

Throughout the 19th century, stress was placed on the primary vaccination of infants as the optimum method of providing protection against smallpox, and laws for compulsory vaccination during the first 3–6 months of life were introduced in many countries. However, in the St Petersburg Foundling Hospital, infants aged 7–8 days were vaccinated with lymph maintained by arm-to-arm vaccination from 1801, when the Empress of Russia obtained lymph from Jenner, until 1867, when vaccine from cows began to be used. There were no serious complications, but a few infants required repeated inoculation before a take was obtained. Compulsory registration made it possible to keep track of foundlings until they were 25 years old, so that observations on the efficacy of vaccination were possible. There were 17 epidemics of smallpox in St Petersburg between 1826 and 1846; out of about 15 000 foundlings, only 34 had smallpox, with only 1 fatality (Fröbelius, 1869; Donnally & Nicholson, 1934). Elsewhere, the vaccination of newborn infants exposed to cases of smallpox was occasionally recommended, but routine vaccination of newborn children in a hospital appears to date from the early 20th century, in some centres in France and Germany. The compulsory vaccination of

Plate 7.6. Lesions in a Pakistani child due to use of the rotary lancet, with insertions at 4 separate sites.

neonates was first practised in Detroit, USA, at the time of an epidemic of variola major in 1925 (Lieberman 1927).

Espmark & Rabo (1965a,b) examined the effect of maternal antibody on the response of infants vaccinated under the age of 1 month. They found that more potent vaccines were needed for these younger infants than for infants vaccinated at 5–12 months of age, but that with potent vaccines ($10^{8.0}TCID_{50}$ per ml or higher) take rates and neutralizing antibody responses were equally good in both groups, and the local signs and constitutional symptoms were milder in the younger infants.

In most countries of Europe and North America, infants were vaccinated during the second 6 months after birth. In the United Kingdom (Conybeare, 1964b) and in the USA (Neff et al., 1967; Lane et al., 1969), investigations into the complications of vaccination indicated that the risk of postvaccinial encephalitis in infants vaccinated before the age of 1 year was greater than that in those vaccinated later. This led to recommendations that vaccination should be postponed until the 2nd year of life. However, in countries in which the maternal antibody level was reasonably high e.g., Sweden it was shown that vaccination in the first 3 months of life was effective, and was usually attended by less severe signs than vaccination later in infancy (Espmark et al., 1973).

Other considerations were important in endemic countries, in which the case-fatality rate for smallpox was very high in young infants. Noting that in Madras, India, most infants were born in hospitals and were accessible as neonates but often difficult to trace after they left hospital, Rao carried out a pilot study in 1959–1960 in which 2500 infants were vaccinated with liquid vaccine on the 3rd day of life, with a take rate of 82% (Rao & Balakrishnan, 1963). Subsequently, take rates of 100% were obtained with freeze-dried vaccine, and the practice of neonatal vaccination was extended to a number of urban areas throughout India (WHO/SE/71.30, Rao).

Interpretation of the Results of Vaccination

In susceptible individuals, smallpox vaccination produced a typical Jennerian pustule at the inoculation site and frequently swelling and tenderness of the draining lymph node. At the height of the reaction there was usually slight fever and the subject might feel indisposed for a few days. A feature of smallpox vaccine, which among the variety of agents now used for immunization against infectious diseases is shared only with BCG vaccine, is that successful vaccination produced a characteristic skin reaction which could be readily observed and which usually left a permanent and characteristic scar. This had both immediate and long-term consequences. Observation of the nature of the cutaneous lesion after recent vaccination or revaccination enabled the vaccinator to decide whether the virus had replicated and the patient had thus been rendered immune to smallpox. In the longer term, the vaccination status of an individual or a population could be determined, with considerable accuracy, by visual examination for vaccination scars, thus obviating the need for a serological survey. For these reasons, special attention was devoted to skin reactions after both primary vaccination and revaccination.

The clinical features of smallpox in unvaccinated and vaccinated persons and the pathogenesis and immune responses in smallpox and after vaccination are described in Chapter 1 and Chapter 3 respectively. It may be useful to recall here the salient features of immunity to smallpox (see box).

Major reaction in primary vaccination

A typical Jennerian pustule was termed a "major reaction", and constituted evidence that the vaccinee would be protected against smallpox. The course of the reaction is illustrated in Plate 7.7A and C. A papule appeared at the vaccination site on the 3rd day after vaccination, and within 2 or 3 days this became vesicular, to constitute the umbilicated and loculated "Jennerian vesicle". As in smallpox (see Chapter 1), the vesicle soon became pustular, owing mainly to the entry of polymorphonuclear cells, the migration of which was stimulated by the viral infection itself, and the surrounding area became erythematous and indurated to a much greater extent than was found in the skin lesions of smallpox. The area of erythema reached a maximum between the 8th and 12th days (usually on the 9th or 10th day), and at this time the draining lymph nodes were enlarged and tender and the subject often sustained a mild fever and may have felt unwell. The pustule dried from the centre outwards to become a dry brown or black scab which fell off about 3 weeks after vaccination, to leave a typical pitted scar.

For routine inspection, observation of the pustule on the 7th day confirmed whether vaccination had been successful. The reaction to vaccinia virus could be readily distinguished from reactions due to bacterial infection, both by its time course and its characteristic appearance.

Revaccination

As described in Chapter 3, successful primary vaccination elicited not only humoral immunity, but also a longer-lasting cell-mediated immunity, which conditioned the response to revaccination. Interpretation of the results of revaccination was sometimes

How Vaccination Protected against Smallpox

A large part of the DNA of all orthopoxviruses is very similar and codes for polypeptides that have a close resemblance in all orthopoxviruses. Vaccination against smallpox consisted in the production of an infection of the skin with vaccinia virus, with extension to the lymph nodes and spleen, organs concerned with the immune response. Because vaccination involved infection of the skin with a relatively large dose of a virus that replicated rapidly, generalization of infection and therefore the immune response occurred more quickly than they did in naturally acquired smallpox. This explains why vaccination during the incubation period of smallpox sometimes aborted or modified the clinical course of the disease.

The immune response to vaccination results in the development of cell-mediated immunity, probably to antigens expressed on the surfaces of infected cells, and a number of humoral antibodies, some of which can neutralize infectivity and may persist for long periods. There are also memory cells for both cell-mediated and humoral immune responses, which wane slowly.

For a few years after vaccination the level of immunity may have been sufficient to prevent completely the replication of variola virus. A somewhat lower level of immunity may have allowed limited replication of variola virus, short of symptom production, but with an anamnestic immune response (subclinical infection). Still lower levels of immunity may have allowed the generalization of variola virus to occur, but stimulation of the memory cells would have produced an accelerated immune response which would have modified the clinical manifestations of smallpox (modified-type smallpox). After many years the immunity provided by vaccination might have waned to such an extent that the attack of smallpox might not have been modified in any way and might indeed have been fatal.

difficult, in terms of evaluating their significance in relation to protection against smallpox. Sometimes there was no reaction at all, a result which was usually due to the use of vaccine of low potency, and which was impossible to interpret correctly (WHO Expert Committee on Smallpox, 1964). If it did occur, the reaction to revaccination could be maximal at any time between the 2nd and the 8th day. During the period before the global smallpox eradication programme, 3 varieties of response used to be distinguished (see, for example, van Rooyen & Rhodes, 1948):

(1) Immediate reaction. Although it used to be described as an "immediate" reaction, dermal hypersensitivity to vaccinial protein produced erythema during the first 24–48 hours after vaccination. It was a classical delayed hypersensitivity reaction, which could be elicited by non-infectious vaccine as well as by active vaccinia virus. Such a response might be given by highly immune individuals even when potent vaccine was used, but it could also occur in individuals with little or no residual immunity who were given inactive vaccine.

(2) Accelerated reaction. Persons with some residual cell-mediated immunity but not enough to inhibit viral replication experienced erythema and the development of a vesicle and sometimes a pustule, which evolved in a sequence more rapid than that seen in a primary vaccination reaction (Plate 7.7B and D). Those with substantial immunity experienced little more than an immediate reaction, whereas those with minimal residual immunity experienced a reaction almost indistinguishable from that seen after primary vaccination. The result of revaccination was dependent on the balance between the potency of the vaccine and residual immunity. A highly potent vaccine could provoke a major reaction, perhaps slightly accelerated, in an individual who had failed to respond to a less potent vaccine; revaccination on the flexor surface of the forearm was more often followed by a substantial reaction than revaccination over the deltoid muscle.

(3) Major reaction in revaccination. If a long period had elapsed after a primary vaccination, revaccination could produce a reaction similar to that described for a primary vaccination. This was called a major reaction.

The WHO Expert Committee on Smallpox (1964) considered that the traditional classification of the reaction to revaccination as "immediate", "accelerated" or "major", as just described, could be misleading, in terms of judging whether an individual might be susceptible to smallpox. The Expert Committee therefore recommended that revaccination should be recorded as successful if, on examination 6–8 days later, there was a pustular lesion or an area of definite induration or congestion surrounding a central lesion, which might be a scab or an ulcer. Such a response was termed a "major reaction". All others were termed "equivocal reactions"—i.e., the persons concerned could not be presumed to be immune to smallpox and were revaccinated.

COMPLICATIONS OF VACCINATION

Smallpox was such a dire disease and the effects of vaccination by comparison so trivial that for a hundred years after vaccination was introduced little account was taken of its complications in places in which smallpox was still endemic. There was a strong anti-vaccinationist movement in several countries, but this was based less on concern about the risks of the procedure than on moral and philosophical objections to compulsory vaccination (see Chapter 6). Among those who supported vaccination there was a reluctance to admit that there were any risks. For example, in the United Kingdom during the first quarter of this century, 103 deaths among 4 275 109 primary vaccinations were recorded as being "associated with vaccination", but the official view was that these "may merely indicate that the child has been vaccinated before death and that death is really attributable to some current illness" (England and Wales, Ministry of Health, 1924). However, smallpox vaccination consisted in the infection of the human host with a virus that must replicate and produce lesions if it was to evoke immunity. Any such procedure that is used on a sufficiently large scale will be associated with occasional cases in which more severe lesions result. The pustular skin lesion illustrated in Plate 7.7 and the fever and lymphadenitis described earlier were the normal results of infection with vaccinia virus. Vaccination was sometimes complicated by much more severe symptoms and was sometimes fatal. These severe complications became a matter of much concern in many industrialized countries, in which endemic smallpox had been eliminated but routine vaccination

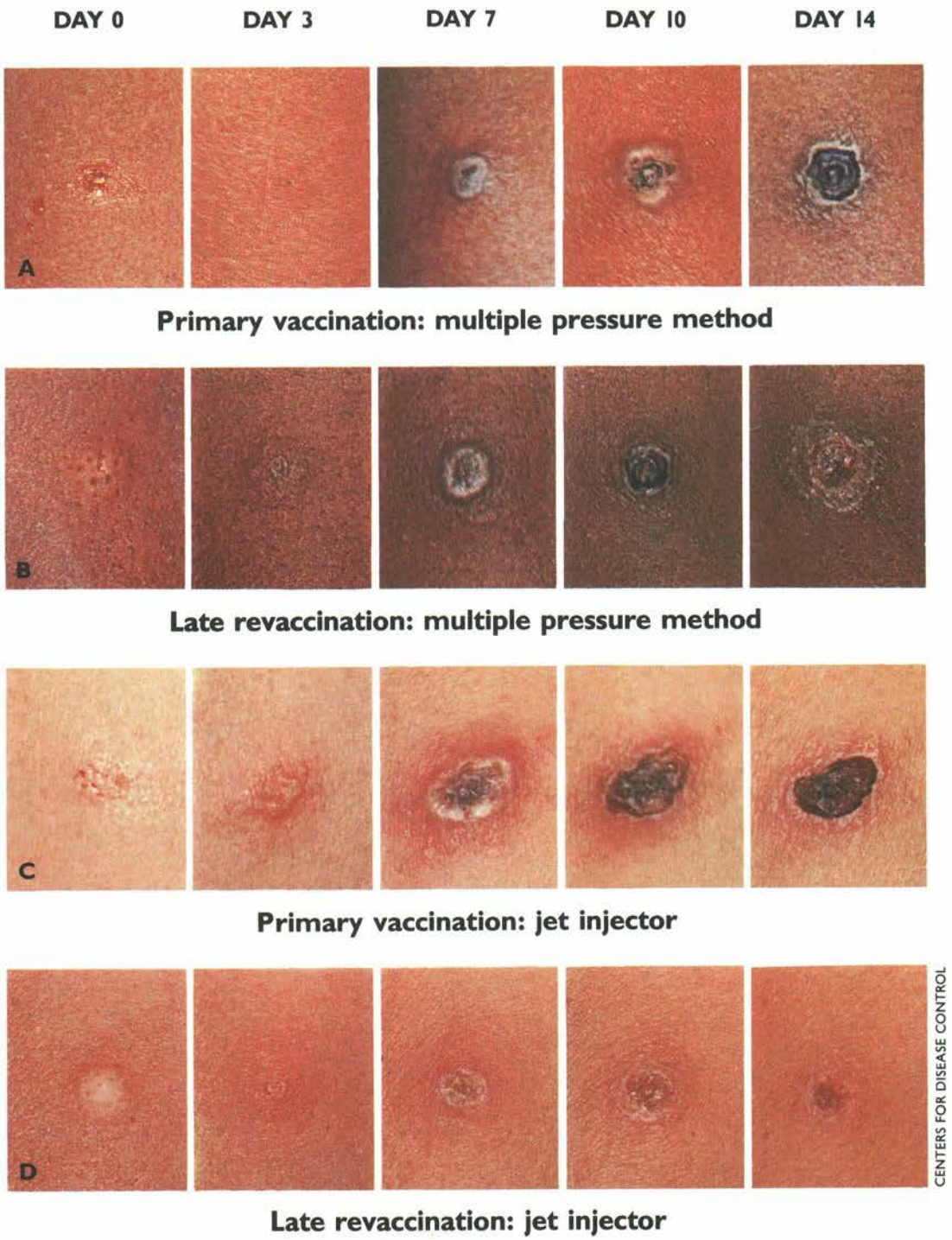


Plate 7.7. Skin reactions after primary vaccination and late revaccination (several years after primary vaccination) by the multiple pressure method and jet injector.

Plate 7.8. Severe complications of vaccination. **A:** Eczema vaccinatum in the unvaccinated contact of a vaccinated sibling. **B:** Progressive vaccinia, which was fatal, in a child with an immunodeficiency. **C:** Generalized vaccinia, 10 days after vaccination; benign course, no scarring. **D:** Auto-inoculation with vaccinia virus.

programmes were maintained in order to protect the community in the event of the importation of smallpox from an endemic area.

Plate 7.9. Abram S. Benenson (b. 1914). United States expert in immunology and communicable diseases, who carried out studies on methods of evaluating responses after vaccination and planned trials of attenuated vaccines. He was a consultant to several WHO committees on smallpox eradication and was instrumental in developing the vaccine production laboratory in Dhaka, Bangladesh.

Types of Complication

Three groups of complications occurred among vaccinated subjects: abnormal skin eruptions, disorders affecting the central nervous system, and a variety of other rarer or less severe complications.

Abnormal skin eruptions

Three kinds of abnormal skin eruption were recognized. Two of them, eczema vaccinatum and progressive vaccinia, were associated with abnormal host reactions; true generalized vaccinia occurred in otherwise healthy persons.

Eczema vaccinatum. This complication occurred in vaccinated persons or unvaccinated contacts who were suffering from or had a history of eczema. Either concurrently with or shortly after the development of the local vaccinial lesion (or after an incubation period of about 5 days in unvaccinated eczematous contacts) a vaccinial eruption occurred at sites on the body that were at the time eczematous or had previously been so. These areas became intensely inflamed, and sometimes the eruption later spread to healthy skin. Constitutional symptoms were severe, with high temperature and generalized lymphadenopathy, and the prognosis was grave in infants in whom large areas of skin were affected (Plate 7.8A).

It was to allow the safe vaccination of children with eczema that Kempe (1968) promoted the use of the CVI-78 attenuated vaccine (see Chapter 11), and vaccinia-immune globulin was often used to treat these cases, in both vaccinated persons and those accidentally infected. The risk of this infection remains, since military personnel continue to be vaccinated in some countries. Several cases of vaccinial infection (and thus potentially of eczema vaccinatum) in contacts of recently vaccinated military personnel were reported in Canada and the United Kingdom, and in the USA as recently as 1985 (*Journal of the American Medical Association*, 1985).

Progressive vaccinia (*vaccinia necrosum*). This complication occurred only in persons who suffered from a deficient immune mechanism, such as agammaglobulinaemia, defective cell-mediated immunity or immunodeficiency associated with tumours of the reticulo-endothelial system or the use of immunosuppressive drugs (see Chapter 3, Fig. 3.8). In these cases the local lesion at the vaccination site failed to heal (Plate 7.8B), secondary lesions sometimes appeared elsewhere on the body and all lesions spread progressively until—as was likely—the patient died, usually 2–5 months later.

Generalized vaccinia. As mentioned earlier, vaccinia virus produced a systemic infection in man, with transient viraemia. Very rarely a generalized vaccinial rash, sometimes covering the whole body, occurred 6–9 days after vaccination (Plate 7.8C). The course of the individual skin lesions resembled that of the lesion at the vaccination site, but if the rash was profuse the lesions sometimes varied greatly in size. The generalized eruption usually did not have the "centrifugal" distribution which was characteristic of the rash of smallpox (see Chapter 1). Generalized vaccinia was not associated with severe immunodeficiency, and the prognosis was good.

Accidental infection. This was the most common complication of vaccination, but it was usually not serious and was certainly greatly

underreported. The commonest sites, in cases that were seen by physicians, were the eyelids (Plate 7.8D), vulva and perineum. Two categories were included in a national survey carried out in the USA (see below and Table 7.3): accidental infection of secondary sites on vaccinees and accidental infection of normal contacts of vaccinated persons.

Postvaccinial tonsillitis

Some Soviet authors (Braginskaya et al., 1971; Gurvich et al., 1974) regard postvaccinial tonsillitis as a not uncommon complication of primary vaccination. Gurvich et al. (1979) reported the recovery of vaccinia virus from pharyngeal swabs in 49% of children with postvaccinial tonsillitis, compared with 7% of those with no complications.

Postvaccinial encephalitis

This was the most serious complication of vaccination in persons in whom there was no contraindication for the procedure. There is an extensive literature on the subject, reviewed by Wilson (1967); the histopathology is described in Chapter 3. One difficulty in assessing postvaccinial encephalitis is that the term encompassed 3 conditions, only 2 of which were due to vaccinial infection (see box).

Concomitant disease. A temporal association does not prove causation, and some cases of encephalitis after vaccination were undoubtedly merely coincident disease due to other causes. For example, Greenberg & Appelbaum (1948) noted that of 49 cases diagnosed ante mortem as postvaccinial encephalitis, 4 out of the 8 fatal cases proved on autopsy to have been due to other causes (2 cases of tuberculous meningitis, 1 brain tumour and 1 case of hypertensive vascular disease). Some of the non-fatal cases may also have been coincidental.

Cases of encephalitis may be expected to occur in any large population of children within a defined period even if no vaccines of any kind are administered. A survey in New Jersey, USA, in 1965 showed that in the absence of vaccination 2.86 cases of encephalitis occurred per million children 1–9 years old per 28-day period; an investigation in Florida in 1968 reported a figure of 2.28 cases per million, in the same age group and during the same time span (Landrigan & Witte, 1973). Figures of a like magnitude were found in the National Childhood Encephalopathy Study in the United Kingdom, undertaken in 1976 because of widespread public and professional concern over the safety of pertussis immunization (England and Wales, Department of Health and Social Security, 1981). The results showed that the majority of the severe neurological disorders studied were not associated with recent immunization (within 28 days) and must be attributed to other causes. Nevertheless, serious neurological complications were sometimes caused by smallpox vaccination, 2 forms being recognized.

Encephalopathy and encephalitis. The pathological distinction made by Vries (1960)

Central Nervous System Disease after Vaccination

"Postvaccinial encephalitis" probably includes several different pathological conditions, of which 3 are specific. First, in any procedure practised as widely as was vaccination against smallpox, there were inevitably some cases of the temporal coincidence of vaccination and some other quite unrelated disease that produced signs of encephalitis. Very rarely, there could be infection of the meninges with vaccinia virus. In infants under 2 years of age there was sometimes a general hyperaemia of the brain, mild lymphocytic infiltration of the meninges, widespread degenerative changes in ganglion cells and occasionally perivascular haemorrhages—what Vries (1960) called postvaccinial encephalopathy. The commonest form, in individuals over 2 years of age, was characterized by perivenous demyelination and microglial proliferation in the demyelinated area, with some lymphocytic infiltration but very little oedema. The pathological features of this form, for which the term "postvaccinial encephalitis" (or "encephalomyelitis") was usually reserved, were similar to those seen in other post-infection encephalitides.

between encephalopathy, in infants under 2 years of age, and postvaccinial encephalitis or encephalomyelitis, with characteristic perivenous demyelination, in individuals over 2 years of age, is important and can be tentatively recognized by consideration of the age of the subject, the symptomatology and the incubation period. According to Spillane & Wells (1964) the onset in cases of encephalopathy was often violent, characterized by convulsions; hemiplegia and aphasia were common, the period of amnesia was short, and the spinal fluid, though under increased pressure, was often normal. Recovery was frequently incomplete, the patient being left with cerebral impairment and hemiplegia.

On the other hand, in the perivenous demyelinating microglial encephalitis following vaccination in subjects over 2 years of age the onset was usually abrupt, with fever, vomiting, headache, malaise, and anorexia, succeeded by such symptoms as loss of consciousness, amnesia, confusion, disorientation, restlessness and delirium, drowsiness, convulsions and coma, with incontinence or retention of urine, obstinate constipation, and sometimes meningismus. Paralysis, when it occurred, tended to be of the upper neuron type. The spinal fluid showed an increase in the concentration of protein and the number of lymphocytes. The case-fatality rate was usually about 35% and in fatal cases death usually occurred within a week. In patients who survived, recovery often set in within a few days and was complete within 2 weeks.

Weber & Lange (1961) found that almost all cases of postvaccinial central nervous system disease in children less than 2 years old and diagnosed as encephalopathy had incubation periods of 6–10 days (mean, 8.6 ± 2.3 days) from the date of vaccination (Table 7.2). By contrast, 96% of 161 cases of postvaccinial encephalitis were in individuals over 2 years of age and most had incubation periods of 11–15 days (mean, 12.3 ± 2.1 days), an interval compatible with an immunopathological basis for the syndrome. In fatal cases, the day of death in infantile encephalopathy was on average 10.5 ± 3.0 days after vaccination; the corresponding figure for encephalitis was 16.3 ± 3.9 days.

Postvaccinial encephalitis began to cause concern in the 1920s and 1930s (Hurst, 1953), when it appeared to be especially frequent in several European countries. As smallpox became less common, the importance of this serious complication of vaccination increased, mainly because there was no way of assessing the risk of postvaccinial encephalitis beforchand—unlike progressive vaccinia and eczema vaccinatum, for which there were known predisposing conditions. No means were known then, or in fact are known now, of predicting the occurrence of post-infection encephalitis, whether attributable to measles, vaccination against rabies, or smallpox vaccination (Johnson, 1982).

Other complications of vaccination

Very rarely, the fetus carried by a woman who had been vaccinated was infected *in utero*. Although a possible example of this was described by Jenner (1809), up to 1978 only 28 cases had been reported in the scientific literature, almost all as single case reports (A. Gromyko, personal communication, 1978). Of the 25 cases for which data are available, 21 occurred in mothers who had been vaccinated during the first 6 months of pregnancy and 4 occurred in mothers vaccinated later. In the first group, a fetus with generalized vaccinia was delivered on average 8 weeks after the vaccination, and in the second group about 4 weeks after vaccination. Many cases were fatal, the fetus being stillborn or dying a few days after birth. There is no convincing

Table 7.2. Length of the incubation period in 259 cases of postvaccinial cerebral damage after primary vaccination[a]

Incubation period (days)	Encephalopathy		Postvaccinial encephalitis	
	Number of cases	%	Number of cases	%
4	2	2.0	0	–
5	3	3.1	2	1.2
6	12	12.2	0	–
7	13	13.3	1	0.6
8	17	17.4	6	3.7
9	24	24.5	8	5.0
10	10	10.2	6	3.7
11	5	5.1	21	13.0
12	3	3.1	37	23.0
13	3	3.1	31	19.3
14	4	4.1	31	19.3
15	1	1.0	12	7.5
16	0	–	3	1.9
17	0	–	1	0.6
18	1	1.0	2	1.2
Total	98	–	161	–
Subjects aged ≤2 years	96	98.0	7	4.3
Subjects aged >2 years	2	2.0	154	95.7

[a] Based on Weber & Lange (1961).

evidence that congenital malformations ever resulted from vaccination of the mother; the infected fetus usually died, but if it survived it recovered completely (Töndury & Foukas, 1964). The mother usually sustained a normal vaccination reaction; the occurrence of fetal vaccinia was additional evidence that viraemia occurred during normal vaccination.

Until smallpox was eradicated, smallpox vaccination was the most widespread immunization procedure in the world. It was thus inevitable that there should sometimes be a temporal coincidence between vaccination and the onset of certain other rare conditions of unknown etiology, such as multiple sclerosis. One rare association that probably had some etiological significance was the occurrence of a malignant skin tumour, such as melanoma, in the smallpox vaccination scar, usually many years after vaccination (Marmelzat, 1968). Vaccinial osteomyelitis was occasionally reported, the diagnosis of which was sometimes confirmed by the recovery of vaccinia virus (Sewall, 1949).

Sometimes vaccines were contaminated with pyogenic cocci, or the introduction of staphylococci into the skin during the vaccination led to localized bacterial infection.

Frequency of Complications

Apart from a multitude of case reports, estimates of the frequency of severe complications—especially postvaccinial encephalitis, which was widely recognized in the 1930s—were produced in many European countries during the period 1940–1965. These have been summarized by Wilson (1967). More useful, because they are more comprehensive, are the two surveys carried out in the USA (nation-wide and in 10 states) by the Communicable Disease Center (CDC—subsequently renamed the Centers for Disease Control), Atlanta, Georgia. Using different methodologies, these surveys were designed to estimate the incidence of all complications of smallpox vaccination in the USA for the year 1968. The methodologies of these two surveys will be described before the frequency of various complications is discussed.

Methodology of the CDC surveys

Following a nation-wide retrospective survey of complications occurring during the year 1963 (Neff et al., 1967), CDC undertook a comprehensive prospective national survey, and a confirmatory, less extensive, survey through physicians in 10 selected states, of the frequency of complications of smallpox vaccination in the USA in the year 1968.

National survey (Lane et al., 1969). Efforts were made to identify all possible complications, on a national scale, using 8 methods to obtain information.

(1) The American Red Cross Vaccinia-Immune Globulin (VIG) distribution system supplied the names of physicians who had been provided with VIG, which was in short supply, for patients. It was distributed from some 10 centres and released to the attending physician only after a telephone conversation with the physician at the Red Cross centre and due justification of its use had been made. The attending physicians were asked for clinical and epidemiological information on their patients shortly after receiving VIG.

(2) Consultants to the Red Cross VIG Program supplied the names of patients suspected of having complications of vaccination who came to their attention but did not receive VIG.

(3) The National Encephalitis Surveillance Program of CDC received reports from each state of all cases of encephalitis, no matter what the cause.

(4) Death certificates citing complications of vaccination were scrutinized.

(5) Casual reports reaching state and territorial epidemiologists regarding vaccination complications that had not been officially reported were transmitted to CDC.

(6) The Burroughs Wellcome Company supplied information on patients who received the drug metisazone (Marboran) for the treatment of complications of vaccination.

(7) Reports were provided by smallpox vaccine producers who had received complaints from patients with complications allegedly attributable to their products.

(8) The Viral Exanthems Unit of CDC reported on specimens submitted to its diagnostic laboratory for the confirmation of vaccinia virus.

The results obtained in this national survey, expressed in absolute numbers and as cases per million vaccinations, are set out in Tables 7.3 and 7.4 respectively.

Ten-state survey (Lane et al., 1970b). Ten states, whose populations constituted 11.6%

of the total population of the USA, were chosen, and information was sought there through mail surveys directed to practising physicians. The states in question were selected partly because of their size (not too large) and partly because of the interest shown by their state epidemiologists and the presence of epidemic intelligence service officers assigned by CDC. Some 84% of physicians responded in 8 of the states and 44% and 49% respectively in the other 2. The questionnaires sought information on any patients with complications of vaccination.

The physicians' diagnoses were accepted for minor complications, but clinical data for more severe complications were thoroughly reviewed and accepted only if the information was considered adequate. The results of this survey are presented in Tables 7.5 and 7.6.

Comparisons of data from different sources

Lack of generally accepted diagnostic criteria, within countries and between countries, as well as variability in the completeness of reporting, makes it difficult to arrive at comparative judgements. Problems of various kinds were associated with each of the important complications. For example, some physicians reported patients who had erythema multiforme accompanying vaccination, or even accidental infection of a site or sites elsewhere on the body, as "generalized vaccinia". Others restricted this term to cases with a generalized rash (Plate 7.8C).

Most important, there were no generally accepted criteria for the diagnosis of postvaccinial encephalitis. In some countries all reports of postvaccinial encephalitis were reviewed by an experienced team; in others the report was based on the views of the attending physician, who might report as encephalitis cases in which convulsions or some other single symptom occurred, or cases with high fever and drowsiness after vaccination. In addition, there were always a few cases of encephalitis due to other causes which were merely coincident with vaccination, a problem that was dealt with in some countries by national encephalitis surveys.

As regards the USA in 1968, significantly more cases of all types of complication were found in the 10-state survey than in the national survey (compare Tables 7.4 and 7.6). This presumably resulted from the more intensive effort to discover all cases of complications made possible by the methodology of the 10-state survey, the data from which provide the better basis for comparison of complication rates in the USA with those in other countries.

Eczema vaccinatum. The CDC national survey recorded 58 cases of eczema vaccinatum among primary vaccinees, 8 among persons who had undergone revaccination and 60, with 1 death, among persons infected by contact. The frequencies were over 3 times higher than this in the 10-state survey (38.5 compared with 10.4 per million after primary vaccination and 3.0 compared with 0.9 per million after revaccination).

Apart from the CDC survey, few data on the frequency of this complication are available. In the mass vaccination campaign that followed the importation of smallpox into New York in 1947, during which 5–6 million people were vaccinated (but childhood eczema was accepted as a contraindication to vaccination), 10 cases of eczema vaccinatum occurred among vaccinees and 28 cases among persons who had not been vaccinated but had been in intimate contact with a recently vaccinated subject (Greenberg, 1948). There was an outbreak of smallpox in South Wales in 1962–1963 and about 900 000 persons were vaccinated. Waddington et al. (1964), who probably saw all patients with severe skin eruptions, recorded 35 cases of eczema vaccinatum (10 in vaccinees, 25 in unvaccinated contacts), with 2 deaths. The authors emphasized that the severity of eczema vaccinatum was independent of the activity of the underlying eczema, which in most patients was quiescent at the time of infection. This suggests that the virus often reached the skin by the haematogenous route, rather than as a result of the direct infection of eczematous lesions.

Progressive vaccinia (*vaccinia necrosum*). Eleven cases of progressive vaccinia were recorded in the CDC national survey. Four of these—all of whom had received vaccinia-immune globulin—were also identified in the 10-state study. In the national survey 6 cases were seen in revaccinated individuals, all of whom showed evidence of serious pre-existing illness, including leukaemia, Hodgkin's disease and lymphoma. Only 1 case occurred in a child, a 22-month-old infant with a congenital immune disorder—Bruton's hypogammaglobulinaemia. There were 4 deaths, despite treatment with vaccinia-immune globulin and metisazone.

Table 7.3. Complications of smallpox vaccination in the USA for the year 1968, as determined by the CDC national survey. Numbers of different kinds of complication by vaccination status and age[a]

Vaccination status and age (years)	Estimated number of vaccinations	Number of cases						
		Post-vaccinial encephalitis[b]	Progressive vaccinia[b]	Eczema vaccinatum[b]	Generalized vaccinia	Accidental infection	Other	Total
Primary vaccination[c]								
<1	614 000	4 (3)	0	5	43	7	10	69
1–4	2 733 000	6	1	31	47	91	40	216
5–9	1 553 000	5 (1)	1 (1)	11	20	32	8	77
10–14	295 000	0	0	1	2	1	1	5
15–19	111 000	0	1 (1)	2	3	2	0	8
⩾20	288 000	1	2	7	13	4	5	32
Age unknown		0	0	1	3	5	2	11
Total	5 594 000	16 (4)	5 (2)	58	131	142	66	418[c]
Revaccination								
<1	0	0	0	0	0	0	0	0
1–4	478 000	0	0	1	0	1	1	3
5–9	1 643 000	0	1 (1)	4	1	3	2	11
10–14	1 440 000	0	0	1	0	0	0	1
15–19	1 217 000	0	1	2	0	0	0	3
⩾20	3 796 000	0	4 (1)	0	9	3	6	22
Total	8 574 000	0	6 (2)	8	10	7	9	40
Contacts								
<1		0	0	4	0	9	1	14
1–4		0	0	38 (1)	1	16	6	61
5–9		0	0	8	0	7	0	15
10–14		0	0	0	0	2	0	2
15–19		0	0	1	0	1	0	2
⩾20		0	0	9	1	9	0	19
Age unknown		0	0	0	0	0	1	1
Total		0	0	60 (1)	2	44	8	114
Grand total	14 168 000	16 (4)	11 (4)	126 (1)	143	193	83	572

[a] From Lane et al. (1969).
[b] Figures in parentheses indicate numbers of deaths attributable to vaccination.
[c] Includes 31 patients with unknown vaccination status.

Table 7.4. Complications of smallpox vaccination in the USA for the year 1968, as determined by the CDC national survey. Data of Table 7.3 expressed as cases per million vaccinations[a,b]

Vaccination status and age (years)	Postvaccinial encephalitis	Progressive vaccinia	Eczema vaccinatum	Generalized vaccinia	Accidental infection	Other	Total
Primary vaccination							
<1	6.5	–	8.1	70.0	11.4	16.3	112.4
1–4	2.2	0.4[c]	11.3	17.2	33.3	14.6	79.0
5–9	3.2	0.6[c]	7.1	12.9	20.6	5.2	49.6
10–19	–	2.5[c]	7.4	12.3	7.4	2.5[c]	32.0
⩾20	3.5[c]	6.9[c]	24.3	45.1	13.9	17.4	111.1
Total	2.9	0.9	10.4	23.4	25.4	11.8	74.7
Revaccination							
<1	–	–	–	–	–	–	–
1–4	–	–	2.1[c]	–	–	2.1[c]	4.2[c]
5–9	–	0.6[c]	2.4	0.6[c]	1.8[c]	1.2[c]	6.7
10–19	–	0.4[c]	1.1	–	–	–	1.5
⩾20	–	1.1	–	2.4	0.8[c]	1.6	5.8
Total	–	0.7	0.9	1.2	0.8	1.0	4.7

[a] From Lane et al. (1969).
[b] Omits 114 patients with contact-acquired vaccinia.
[c] Rate computed on the basis of 3 cases or less.

Conybeare (1964a) reported 8 cases of progressive vaccinia (with 7 deaths) among 5 million vaccinees in England and Wales over the years 1951–1960. All occurred after the primary vaccination of infants less than 6 months old, most of whom were probably suffering from congenital immunodeficiencies.

Generalized vaccinia. Being a relatively mild condition, generalized vaccinia was recorded much more frequently in the 10-state than in

Table 7.5. Complications of smallpox vaccination in 10 states of the USA for the year 1968. Numbers of different kinds of complications by age and vaccination status[a]

Vaccination status and age (years)	Estimated number of vaccinations	Post-vaccinial encephalitis	Progressive vaccinia	Eczema vaccinatum	Generalized vaccinia	Accidental infection	Erythema multiforme	Other	Total
Primary vaccination[b]									
<1	71 000	3	0	1	28	36	31	11	110
1–4	317 000	3	1	14	74	183	50	75	400
5–19	229 000	2	0	8	32	85	20	49	196
⩾20	33 000	0	0	1	7	20	1	21	50
Age unknown	..	0	0	1	16	20	5	17	59
Total	650 000	8	1	25	157	344	107	173	815[b]
Revaccination									
<1	0	0	0	0	0	0	0	0	0
1–4	55 000	0	0	0	0	6	4	1	11
5–19	503 000	0	0	1	5	24	1	12	43
⩾20	440 000	2	3	2	4	11	4	24	50
Age unknown	..	0	0	0	0	1	1	2	4
Total	998 000	2	3	3	9	42	10	39	108
Contact									
<1		0	0	0	0	1	0	1	2
1–4		0	0	4	1	12	1	0	18
5–19		0	0	6	0	5	0	0	11
⩾20		0	0	3	0	11	0	0	14
Age unknown		0	0	0	0	0	0	0	0
Total		0	0	13	1	29	1	1	45
Grand total	1 648 000	10	4	41	167	415	118	213	968

[a] From Lane et al. (1970b).
[b] Includes 65 patients with unknown vaccination status.

Table 7.6. Complications of smallpox vaccination in 10 states of the USA for the year 1968. Data of Table 7.5 expressed as cases per million vaccinations[a,b]

Vaccination status and age (years)	Post-vaccinial encephalitis	Progressive vaccinia	Eczema vaccinatum	Generalized vaccinia	Accidental infection	Erythema multiforme	Other	Total
Primary vaccination								
<1	42.3	–	14.1	394.4	507.0	436.6	154.9	1 549.3
1–4	9.5	3.2	44.2	233.4	577.3	157.7	236.6	1 261.8
5–19	8.7	–	34.9	139.7	371.2	87.3	214.0	855.9
⩾20	–	–	30.3	212.1	606.1	30.3	636.4	1 515.2
Total[c]	12.3	1.5	38.5	241.5	529.2	164.6	266.2	1 253.8
Revaccination								
<1	–	–	–	–	–	–	–	–
1–4	–	–	–	–	198.1	72.7	18.2	200.0
5–19	–	–	2.0	9.9	47.7	2.0	23.9	85.5
⩾20	4.5	6.8	4.5	9.1	25.0	9.1	54.5	113.6
Total[d]	2.0	3.0	3.0	9.0	42.1	10.0	39.1	108.2

[a] From Lane et al. (1970b).
[b] Omits 45 patients with contact-acquired vaccinia.
[c] Total includes 59 patients of unknown age.
[d] Total includes 4 patients of unknown age.

the national survey in the USA (241.5 per million primary vaccinations compared with 23.4 per million among the same group in the national survey). Generalized vaccinia was rare in persons undergoing revaccination.

Conybeare (1964a) recorded 162 cases in about 5 million vaccinations and revaccinations carried out in England and Wales in 1951–1960. The lesion at the vaccination site matured normally, but 9–14 days after vaccination papular lesions appeared elsewhere on the body; these became vesicular and then pustular before scabbing. On any individual patient the lesions usually varied considerably in size. One hundred and fifty cases occurred in primary vaccinees and 106 in infants less than 1 year old. The accompanying constitutional disturbance was mild.

Accidental infection. Not surprisingly, many cases of accidental infection were not re-

ported and therefore did not figure in the CDC national survey. The rates in the 10-state survey were about 20 times higher (25.4 per million primary vaccinations in the national survey; 529.2 per million in the 10-state survey). Very few cases occurred after revaccination.

A special kind of accidental infection on which some statistics were collected was that associated with ocular lesions (Plate 7.8D). Sedan et al. (1953) recorded 19 cases among 850 000 vaccinees in Marseilles in 1952 (22.3 per million), and Waddington et al. (1964) noted 11 cases of vaccinia on the eyelid among 900 000 vaccinees in South Wales in 1962. The most comprehensive report (Ruben & Lane, 1970), derived from cases detected by the perusal of requests for vaccinia-immune globulin addressed to the American Red Cross, records 348 cases, most of which came to light in the years 1963 and 1968, when special national surveys had been conducted. There were also some cases that occurred in 1964, 1965 and 1969. Corneal involvement occurred in 22 cases and produced a much higher rate of residual ocular defect (Table 7.7).

Table 7.7. Vaccination status of subjects with ocular vaccinia[a]

Vaccination status	Number of cases	
	Without corneal involvement	With corneal involvement
Primary vaccination	229	15
Revaccination	14	1
Contact infection	60	6
Unknown	23	0
Total	326 (7)[b]	22 (4)[b]

[a] Based on Ruben & Lane (1970).
[b] Figures in parentheses indicate numbers of cases showing residual defects.

Postvaccinial encephalitis. Although comparisons of data were difficult because of the variability of the criteria for making the diagnosis and the extent of reporting, the frequency of postvaccinial encephalitis varied greatly in different countries. Table 7.8 presents data from 5 countries (9 series of studies) which illustrate dramatically the large differences reported, especially for postvaccinial encephalitis after the primary vaccination of individuals over 2 years of age. All the statistics presented probably include a few cases of encephalitis that were merely coincident with, rather than caused by, vaccination, but the differences in frequencies are so great that they could not have been due solely to diagnostic or statistical eccentricities.

Postvaccinial encephalitis was much more common in European countries than in the USA, and more common in the countries of continental Europe than in the United Kingdom. There were also differences in the age incidence. In most countries postvaccinial encephalitis was considered mainly a risk of primary vaccination in adolescents or young adults, but in the USA the higher incidence of encephalopathy in infants under the age of 1 year led to a recommendation that compulsory vaccination should be postponed until the 2nd year of life. More detailed analysis of the data used in Table 7.8 for various age groups showed that the frequency of postvaccinial encephalitis was greatest in the age group 6–12 years.

Wilson (1967) summarized data from many sources which demonstrate that the case-fatality rate for most series of cases of postvaccinial encephalitis was about 30%, with a reported low of 9% and a high of 57%.

Although host factors were certainly involved in a disease believed to have an immunopathological basis (see Chapter 3), the strain of virus appears to have been important in determining the frequency of postvaccinial encephalitis. The New York City Board of Health strain, which was the principal strain used in the USA, appears to have been the least likely of the widely used strains to cause it, closely followed by the Lister strain. Indeed, the frequencies recorded by Neff et al. (1967) and Lane et al. (1969) for individuals over 1 year of age were so low that they could almost be accounted for by the coincident occurrence of encephalitis due to other causes. However, the rate was much higher in the 10-state survey reported by Lane et al. (1970b).

Although there is no single laboratory test that can satisfactorily determine the virulence of vaccinia virus for man or assess the likelihood that vaccination will cause postvaccinial encephalitis, investigations by Marennikova et al. (1969) in mice and rabbits were consistent with the following classification of several strains in terms of their pathogenicity: mildly pathogenic—New York City Board of Health and EM-63; moderately pathogenic—Lister, Bern and Patwadangar; and highly pathogenic—Copenhagen, Tashkent and Ikeda (see Chapter 11, Table 11.20).

Table 7.8. Incidence of postvaccinial encephalopathy (in infants under 2 years of age) and postvaccinial encephalomyelitis (in individuals over 2 years of age) after primary vaccination, in various places and at various times[a]

Place, date (investigator)	Encephalopathy		Encephalomyelitis	
	Age less than 2 years		Age more than 2 years	
	Number of cases/ Number of vaccinations	Number of cases per million	Number of cases/ Number of vaccinations	Number of cases per million vaccinations
Netherlands, 1924–1928 (van den Berg, 1946)	6/155 730	39	127/548 420	232
Netherlands, 1940–1943 (Stuart, 1947)	22/441 294	50	56/160 775	348
Düsseldorf, 1948 (Femmer, 1948; Stuart, 1947)	0/28 768	0	14/67 068	209
Bavaria, 1945–1953 (Herrlich, 1954)	51/1 008 000	56	17/140 800	121
Austria, 1948–1953 (Berger & Puntigam, 1954)	6/58 438	103	26/21 323	1 219
Hamburg, 1939–1958 (Seelemann, 1960)	34/367 390[b]	93	12/26 713[c]	449
England and Wales, 1951–1970 (Dick, 1973)[d]	51/3 730 000	13	76/7 620 000	10
USA, 1968: national survey (Lane et al., 1969)	4/614 000[e]	7	12/4 980 000[f]	2
USA, 1968: 10-state survey (Lane et al., 1970b)	3/71 000[e]	42	5/579 000[f]	9

[a] Based on Wilson (1967) and Lane et al. (1969, 1970b).
[b] Age less than 4 years.
[c] Age 4 years or more.
[d] From Conybeare (1964b), 1951–1960 and J. Barnes (upublished observations), 1961–1970.
[e] Age less than 1 year.
[f] Age 1 year or more.

Several different strains of vaccinia virus were used in Belgium and the Netherlands during the 1950s; the incidence of postvaccinial encephalopathy in infants dropped substantially after the Lister strain was introduced in the Netherlands in 1963 (Table 7.9). In Switzerland and Austria the number of reported cases of postvaccinial encephalitis fell dramatically after the Bern strain was replaced by the Lister strain in 1962 and 1967 respectively (C. Fleury, personal communication, 1967; Berger & Heinrich, 1973).

Contraindications to Vaccination

During smallpox eradication programmes in areas in which smallpox was endemic, WHO recommended that no contraindications to vaccination should be envisaged—for two reasons. First, the risk of smallpox infection was considered to be significantly greater than the risk of complications and, secondly, most vaccinations were carried out by personnel without medical training, who could not be expected to diagnose correctly conditions such as eczema. However, it was recommended that very sick individuals should not be vaccinated, because their subsequent death might be attributed to vaccination. On the other hand, in countries in which smallpox was not endemic, special attention was paid to contraindications to vaccination. Instructions as to what physical conditions should be regarded as constituting contraindications varied according to national health legislation, but the following 4 conditions were generally accepted:

(1) Immune disorders. These included agammaglobulinaemia, hypogammaglobulinaemia, neoplasms affecting the reticuloendothelial system and the use of immunosuppressive drugs. Such conditions substantially enhanced the risk of the most serious complication of vaccination—namely, progressive vaccinia.

(2) Eczema. Vaccination was contraindicated in persons who were currently suffering from eczematous skin lesions or whose family included an individual with eczema, because of the risk of eczema vaccinatum in either the vaccinee or the family member concerned. However, it was always difficult to exclude from vaccination persons

Table 7.9. Cases of encephalopathy after the vaccination of infants less than 1 year of age in the Netherlands, 1959–1970[a]

Period	Number of vaccinations	Vaccinia strain	Number of cases[b]	Number of cases per million vaccinations
1959–1962	821 000	Copenhagen	31 (16)	37.7
1963–1970	1 708 000	Lister	19 (11)	11.1

[a] Based on Polak (1973).
[b] Figures in parentheses indicate numbers of deaths.

who had suffered from eczema in the past but did not have active skin lesions; such persons sometimes experienced eczema vaccinatum.

(3) Pregnancy. It is a general principle to avoid immunization in pregnancy. This policy was followed with smallpox vaccination, because of the risk (admittedly rare) of fetal vaccinia, a usually fatal condition.

(4) Disorders of the central nervous system. In order to minimize the risk of postvaccinial encephalitis, disorders of the central nervous system in the person to be vaccinated, or in family contacts, were accepted as contraindications in many countries. However, there is no evidence that the exclusion of such subjects affected the incidence of that complication.

In addition to the above 4 generally accepted contraindications, in some countries vaccination was considered undesirable for persons with an acute infectious disease (influenza, measles, etc.), a chronic infectious disease (e.g., tuberculosis) or an allergic constitution, or for persons who had been immunized against other diseases such as yellow fever, cholera, or typhoid fever on the same day as the scheduled smallpox vaccination. The justifications were, respectively, the hypothetical risk of complications arising from infection with vaccinia virus in persons whose physical condition was not normal at the time, and the belief that an interaction between the different immunizing agents might prevent the occurrence of a proper immunological response.

In most countries in which smallpox was endemic, leprosy was also present. Since primary smallpox vaccination often precipitated reactions such as erythema nodosum leprosum or neuritis in leprosy patients (Webster, 1959), health officers in these areas had to determine whether patients with lepromatous symptoms should be vaccinated. The WHO recommendation was that leprosy, including lepromatous leprosy, should not be a contraindication in such circumstances, since the risk of smallpox infection was substantially greater than that posed by the reactions concerned (Browne & Davis, 1962).

Prevention and Treatment of Complications

Immunoprophylaxis and immunotherapy

Human antivaccinia immunoglobulin (vaccinia-immune globulin), prepared from the plasma of recently vaccinated persons, became available in the early 1950s. Potency requirements were that it should contain at least 500 IU of vaccinia antibody per ml, in terms of the International Standard for Anti-Smallpox Serum (WHO Expert Committee on Biological Standardization, 1967).

It was thought that since some of the more severe complications of vaccination were caused by defects in antibody production, the administration of vaccinia-immune globulin at the time of vaccination might prevent such complications, without inhibiting an active immune response. Nanning (1962) reported on a field experiment in the Netherlands in which about 100 000 army recruits were vaccinated, half of them given vaccinia-immune globulin and the other half a placebo. There were 3 cases of central nervous system complications in the vaccinia-immune globulin group and 13 in the placebo group. No study of similar magnitude was conducted elsewhere, but in the Netherlands vaccinia-immune globulin was subsequently used in all primary vaccinations of adults (Polak, 1973). Vaccinia-immune globulin was also recommended for the prevention of eczema vaccinatum, being administered at the time of vaccination, whenever an eczematous child had to be vaccinated because of special circumstances, such as exposure to a case of smallpox (Sharp & Fletcher, 1973).

Kempe (1960) analysed 300 cases of severe complications of vaccination treated with vaccinia-immune globulin. There was no evidence that it influenced the course of

postvaccinial encephalitis, but observations on 132 treated cases of eczema vaccinatum suggested that it reduced the mortality from the usual level of 30–40% to 7%. It was also useful in treating 28 cases of accidental autoinoculation with vaccinia virus, and led to the prompt cessation of the development of new lesions in 62 patients with generalized vaccinia. However, vaccinia-immune globulin was much less effective in treating cases of progressive vaccinia, because the major immunodeficiency in these cases was in cell-mediated immunity. Vaccinia-immune globulin administration was associated with the production of neutralizing antibody in cases of eczema vaccinatum, generalized vaccinia and progressive vaccinia. Kempe treated all subjects who presented, holding that the cases were few in number and occurred only sporadically and that the early indications of the value of the treatment made it ethically difficult to withhold its use. In another study, Sharp & Fletcher (1973) observed rapid improvement within 48 hours of the administration of vaccinia-immune globulin to cases of generalized vaccinia, eczema vaccinatum and severe local vaccinial reactions.

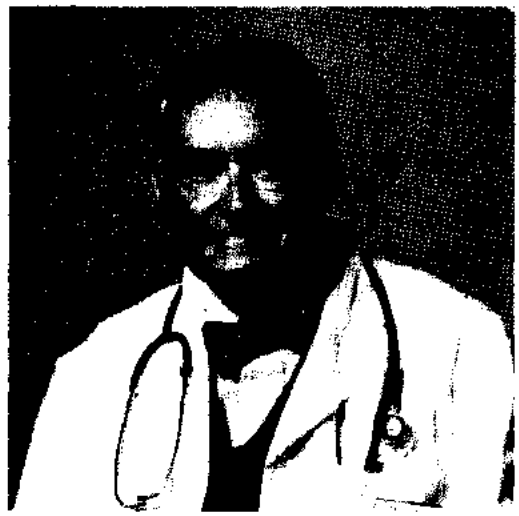


Plate 7.10. C. Henry Kempe (1922–1984). As Professor and Chairman of the Department of Pediatrics at the University of Colorado Medical Center, Denver, USA, Kempe was a major figure in the investigation of complications of vaccination in children in the USA during the 1950s and 1960s. He also participated in the extensive investigations of smallpox carried out with Dr A.R. Rao in Madras, India, over the same period.

Chemotherapy

In the 1950s and 1960s several chemicals were found to inhibit vaccinia virus replication in cell cultures and in laboratory animals. In addition to being investigated for the treatment of smallpox (see Chapter 1), they were tested for the treatment of complications of vaccination. The most effective substances in experimental systems were derivatives of cytosine arabinoside, rifampicin, a urea derivative of diphenyl sulfone, and a thiosemicarbazone derivative termed metisazone (*N*-methylisatin β-thiosemicarbazone). There was no evidence that any of them was effective, although Brainerd et al. (1967) reported that the use of metisazone had a beneficial effect in progressive vaccinia, a condition in which vaccinia-immune globulin was useless.

Reconsideration of Vaccination Policies in Non-endemic Countries

As smallpox transmission was interrupted in various countries, the occasional untoward results of routine vaccination gradually emerged as a public health problem, which concerned both the general public and health administrators. In essence, in smallpox-free countries routine vaccination was maintained or mass vaccination campaigns were undertaken in order to maintain a protective barrier against the spread of smallpox in the population, but this community benefit was gained at the expense of a few individuals who suffered from the complications of vaccination. For example, the last case of smallpox in the USA was reported in 1949 but routine vaccination continued until 1972. The national survey of vaccination in the USA during 1963 carried out by CDC (Neff et al., 1967) showed that among the 14 million persons who were vaccinated against smallpox in that year (6.2 million primary vaccinations and 7.8 million revaccinations), there were 132 cases of severe complications and 7 deaths. From the results of this survey, it could be roughly estimated that between 1949 and 1972 there may have been about 3000 cases of severe vaccinial complications, with some 150 deaths.

Lane & Millar (1969) compared the projected number of deaths from routine vaccination in the USA for the 30 years from 1970 to 2000 with what might be expected if this

procedure were replaced by vaccination of only high-risk groups (military draftees, hospital workers and international travellers), in combination with ring vaccination of contacts (at most 5000 per importation) and occasional mass vaccination campaigns to control smallpox outbreaks resulting from importations. They concluded that there might be 210 vaccination deaths if routine vaccination were continued, compared with 60 deaths from the vaccination of high-risk groups. There would have to be 21 separate importations of smallpox to make up the difference of 150 deaths; but no cases had been imported into the USA during the previous 20 years and the risk was constantly diminishing. Dick (1973) carried out a similar kind of calculation for the United Kingdom and concluded that on the basis of the mortality due to vaccination in that country there would be 150 such deaths if routine vaccination were continued—a figure that would be equalled by the number of smallpox deaths only if there were 50 importations of variola major over the 30 years between 1970 and 2000, compared with the 13 which had occurred during the preceding 20 years. It is clear that routine vaccination in the United Kingdom and the USA, and by analogy in other countries which had long since eliminated smallpox, entailed a cost which had been acceptable when there was a substantial risk of smallpox, either endemic or imported, but which was not justified when the risk had become very slight.

Aside from the risks inherent in routine vaccination, complications posed a severe problem when a country in which smallpox was not endemic conducted mass vaccination for the containment of an outbreak following an importation. For example, in 1963 smallpox was imported into Sweden from an unidentified Asian country. Twenty-seven cases resulted. A voluntary mass vaccination campaign was performed in which about 300 000 persons in central Stockholm were vaccinated in the course of a few weeks (Ström & Zetterberg, 1966). As a result of the vaccination campaign, 77 persons suffered vaccinial complications (neurological complications, 14; carditis, 7; eczema vaccinatum, 7; and postvaccinial exanthema, 49). Without vaccination, of course, there would have been many more than 27 cases of smallpox.

These experiences provoked substantial debate among research workers and health planners during the 1960s as to whether it was justified to continue routine smallpox vaccination in countries in which smallpox was no longer endemic (Benenson, 1974; Dick, 1966, 1971, 1973; Kempe & Benenson, 1965; Langmuir, 1974). This was not a new debate. In the geographically isolated country of Australia compulsory vaccination had been adopted in only 2 of the 6 states, and Cumpston (1914) calculated that only about 30% of the children born in Australia between 1860 and 1910 had ever been vaccinated. "Conscience clauses" introduced into legislation enacted in the states in which compulsory vaccination of infants was operative reduced the proportion of newborn infants vaccinated each year to less than 10% by 1923 (Cumpston & MacCallum, 1925). The responsible state and Commonwealth health officers repeatedly inveighed against this laxity in vaccination, but the state governments took no action. The situation in New Zealand was similar. The threat of smallpox was never perceived as great enough to justify the enforcement of an unpopular measure, and even the large outbreak of variola minor in New South Wales in 1913–1917 (see Chapter 8) was not enough to cause the parliament of that state to pass a compulsory vaccination act.

By the late 1960s, several countries of Europe and those of North America had already discontinued compulsory routine smallpox vaccination programmes, but it was still common for paediatricians to recommend that children should be vaccinated, usually during the 2nd year of life. The reason for this recommendation was that it was believed that complications were less common when primary vaccination was carried out in childhood; moreover, the International Health Regulations, as applied in many non-endemic countries, made the possession of a valid smallpox vaccination certificate almost a *sine qua non* for international travel.

Complications: the Overall Picture

The complications arising from vaccination against smallpox clearly posed a serious public health problem in the non-endemic countries. Several steps were taken to mitigate its effects, notably the substitution of "milder" strains of vaccinia virus, such as the New York City Board of Health and the Lister strains, that caused fewer complications, the

postponement of vaccination until the 2nd or 3rd year of life (which greatly reduced the risk of postvaccinial encephalopathy), the use of vaccinia-immune globulin for the treatment of complications and the development of more attenuated strains of vaccinia virus (see Chapter 11). Nevertheless, there was an irreducible minimum rate of complications, and even normal primary vaccination was associated with unpleasant local and general reactions. The ultimate solution was the discontinuation of vaccination, which could be done without argument only if smallpox were eradicated globally. In addition, universal discontinuation of smallpox vaccination would result in a substantial saving in health budgets covering vaccination programmes and the medical care of patients suffering from complications. These considerations had begun to preoccupy the world scientific community during the 1950s and 1960s, and constituted one of the reasons for promoting the development of the global smallpox eradication programme.

PROGRAMMES FOR VACCINATION AND REVACCINATION

Vaccination and Revaccination of the General Public

By the middle of the 20th century, smallpox vaccination had become part of the routine immunization programme of most countries in the world. The recommended age for vaccination varied from country to country, but it was common practice for primary vaccination to be done during the first 2 years of life and revaccination performed when children entered and left primary school. The first report of the WHO Expert Committee on Smallpox (1964) recommended that in countries in which smallpox was endemic, primary vaccination should be carried out as early as possible, preferably in the neonatal period, and repeated about 12 months later. For revaccination, a 5–10 year interval was recommended for the non-endemic countries and one of 3 years for the endemic countries. In North America and some European countries, hospital staff were, in theory, obliged to be vaccinated every 3 years, but as smallpox faded from memory this requirement was rarely enforced.

Because of the relatively high incidence of postvaccinial encephalopathy among infants in the USA revealed by the CDC surveys, it was recommended that primary vaccination should not ordinarily be carried out during the first 2 years of life. On the other hand, public health experts in many European countries, noting that the highest incidence of postvaccinial encephalitis was in adolescents undergoing primary vaccination, recommended that this immunization should be performed during the 2nd year of life.

Simultaneous Vaccination with Several Antigens

Smallpox vaccination was often carried out at approximately the same time as immunization with diphtheria and tetanus toxoid or with inactivated antigens of pertussis, typhoid and poliomyelitis, since it was considered that such a practice was safe and did not interfere with the immune responses to each agent (Winter et al., 1963). However, it was important not to use the same arm for the injection of bacterial antigens as had been used for the inoculation of smallpox vaccine a few days earlier, in order to avoid the severe febrile reactions that occasionally resulted (A. S. Benenson, personal communication, 1982).

Studies were carried out during the 1950s and 1960s to find out whether the combined use of various live vaccines would affect their safety and efficacy. The simultaneous administration of oral poliovaccine and smallpox vaccine caused no particular problems either in terms of increased side-effects or reduced take rates (Karchmer et al., 1971; Winter et al., 1963). Other studies showed that combinations of smallpox vaccine, BCG vaccine (Lin, 1965), yellow fever vaccine (Meers, 1960), and measles vaccine (Breman et al., 1975) were safe and produced good immune responses. In these studies, separate vaccines were administered simultaneously at different sites. However, when smallpox, measles and yellow fever vaccines were combined and inoculated by jet injection into the same site, there were no untoward effects but the immune response for yellow fever virus was reduced (Meyer et al., 1964b). When smallpox, yellow fever, measles and diphtheria-pertussis-tetanus (DPT) vaccines were administered at separate sites by jet injection, the response to smallpox vaccine was unaffected but the measles seroconversion rate dropped from 89% (if DPT was not given) to 70% (Ruben et al., 1973). However, this apparent decrease

was not observed in later studies, and simultaneous administration of the antigens commonly used in developing countries in the 1970s was generally regarded as safe and efficacious (Foege & Foster, 1974). In practice, the commonest combinations were smallpox and yellow fever vaccines (in much of francophone Africa) and simultaneous immunization against smallpox and measles, in the CDC-assisted programme in western and central Africa (see Chapter 17). Smallpox and BCG vaccinations were given simultaneously but in opposite arms in many countries in central and eastern Africa.

Vaccination of International Travellers

The 1944 International Sanitary Convention (United Nations Relief and Rehabilitation Administration, Health Division, 1945) amended the previous Convention, formulated in 1926, and devised a vaccination certificate (Plate 7.11), which required that the vaccinial reaction should be inspected 8–14 days after the primary vaccination and 48 hours after revaccination. A certificate was not valid for more than 3 years.

On 9 April 1951, a special committee on the drafting of the International Sanitary Regulations (the former International Sanitary Conventions) met in Geneva (World Health Organization, 1951a). During the Committee's sessions, the original draft form of the vaccination certificate was extensively amended (World Health Organization, 1951b; Plate 7.12A). As revised (Plate 7.12B), this form was adopted by the Fourth World Health Assembly on 25 May 1951. When, in 1981, the vaccination of travellers against smallpox was no longer a requirement a stamp was used to cancel the smallpox vaccination certificate but the form was still in use for other vaccination requirements. In 1983 it was replaced by a new form lacking any provision for smallpox vaccination (see Chapter 28, Plate 28.1).

As early as 1945, the authorities concerned with the International Sanitary Convention stipulated that, in relation to vaccination certificates, "recent vaccination shall be taken as meaning evidence of successful vaccination not more than 3 years or less than 14 days previously, or evidence of an immune reaction" (United Nations Relief and Rehabilitation Administration, Health Division, 1945). In 1956, the WHO Committee on International Quarantine noted that although these rules "may lack a firm scientific basis, they are nevertheless administratively expedient in order to avoid delay to persons on an international voyage" (World Health Organization, 1956). The maximum interval of 3 years, in particular, lacked a carefully documented basis, although Marsden (1936) had discovered no cases of variola minor in persons vaccinated less than 7 years earlier, and before that Hanna (1913) had found that variola major was rare and mild in children under 4 years of age who had been vaccinated in infancy, but severe (case-fatality rate, 45%) in unvaccinated children in that age group (see Chapter 1, Table 1.11). Subsequently, Rao (1972) reported that only 90 out of 2181 cases of variola major in children under 4 years of age occurred in those with a vaccination scar.

Nyerges et al. (1972) reported that the levels of neutralizing antibody 3 years after the last revaccination were as high as those found 3 weeks after primary vaccination. Taking the absence of rises in the level of

International Sanitary Convention, 1944.

INTERNATIONAL CERTIFICATE OF VACCINATION AGAINST SMALLPOX

THIS IS TO CERTIFY THAT .....
(Age ..... Sex .....) whose signature appears below has this day been vaccinated by me against smallpox.
Origin and Batch No. of vaccine .....

Official Stamp

Signature of Vaccinator .....
Official Position .....
Place ..... Date .....

Signature of person vaccinated .....
Home Address .....

Important Note: In the case of primary vaccination the person vaccinated should be warned to report to a medical practitioner between the 8th and 14th day, in order that the result of the vaccination may be recorded on this certificate. In the case of revaccination the person should report within 48 hours for first inspection in order that any immune reaction which has developed may be recorded.

THIS IS TO CERTIFY THAT the above vaccination was inspected by me on the date(s) and with the result(s) shown hereunder:

Date of Inspection	*Result*
.....	.....
.....	.....
.....	.....

Official Stamp

Signature of Doctor .....
Official Position .....
Place ..... Date .....

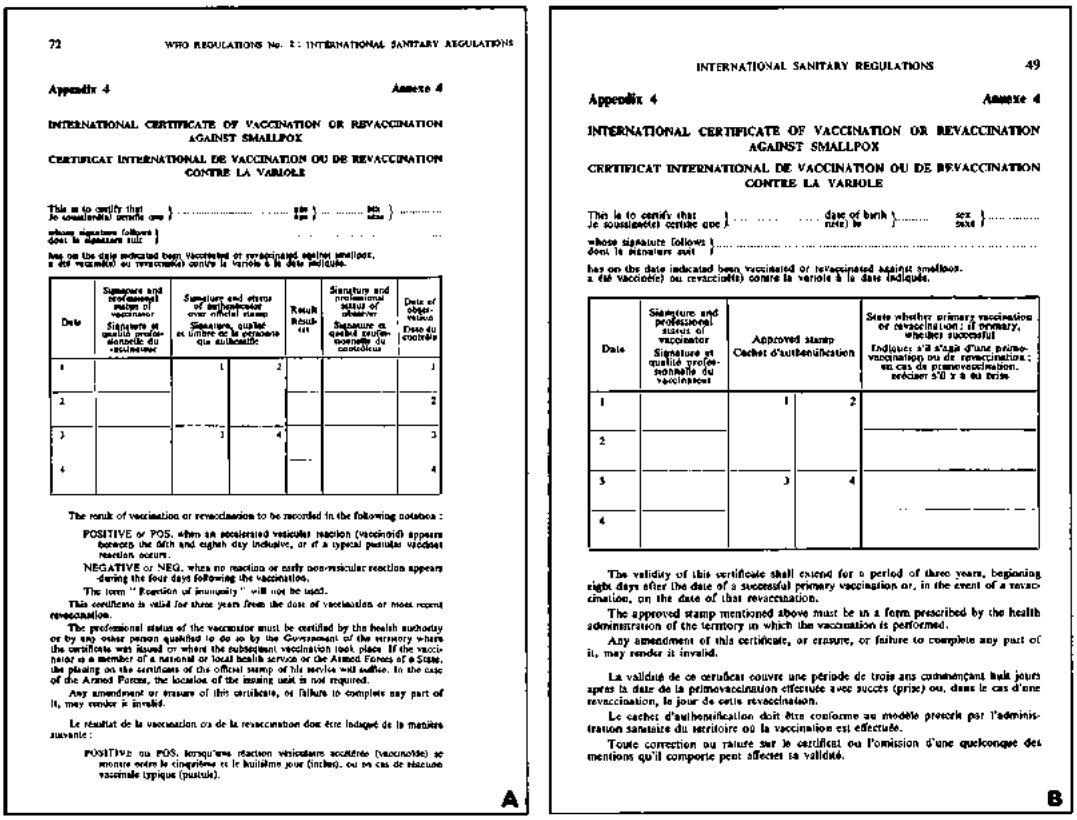
Use one or other of the following terms in stating the result, viz: "Reaction of immunity," "Accelerated reaction (vaccinoid)," "Typical primary vaccinia." A certificate of "No reaction" will not be accepted.

Signature of person vaccinated .....

(This certificate is not valid for more than 3 years from date of issue).

40

Plate 7.11. The first International Certificate of Vaccination against Smallpox, developed by the International Sanitary Convention in 1944.



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Appendix 4 Annexe 4

INTERNATIONAL CERTIFICATE OF VACCINATION OR REVACCINATION AGAINST SMALLPOX

CERTIFICAT INTERNATIONAL DE VACCINATION OU DE REVACCINATION CONTRE LA VARIOLE

This is to certify that / Je soussigné(e) certifie que) ..... née le / ...) sex / sexe) .....

whose signature follows / dont la signature suit) .....

has on the date indicated been vaccinated or revaccinated against smallpox. / a été vacciné(e) ou revacciné(e) contre la variole à la date indiquée.

Date	Signature and professional status of vaccinator / Signature et qualité professionnelle du vaccinateur	Signature and stamp of authenticator / Signature, qualité et timbre de la personne qui authentifie		Result / Résultat	Signature and professional status of observer / Signature et qualité professionnelle du contrôleur	Date of observation / Date du contrôle
1		1	2			1
2						2
3		3	4			3
4						4

The result of vaccination or revaccination to be recorded in the following notation :

POSITIVE or POS. when an accelerated vesicular reaction (vaccinoid) appears between the fifth and eighth day inclusive, or if a typical pustular vaccinal reaction occurs.

NEGATIVE or NEG. when no reaction or only non-vesicular reaction appears during the four days following the vaccination.

The term " Reaction of immunity " will not be used.

This certificate is valid for three years from the date of vaccination or most recent revaccination.

The professional status of the vaccinator must be certified by the health authority or by any other person qualified to do so by the Government of the territory where the certificate was issued or where the subsequent vaccination took place. If the vaccinator is a member of a national or local health service or the Armed Forces of a State, the placing on the certificate of the official stamp of his service will suffice. In the case of the Armed Forces, the location of the issuing unit is not required.

Any amendment or erasure of this certificate, or failure to complete any part of it, may render it invalid.

Le résultat de la vaccination ou de la revaccination doit être indiqué de la manière suivante :

POSITIVE ou POS. lorsqu'une réaction vésiculaire accélérée (vaccinoïde) se montre entre le cinquième et le huitième jour (inclus), ou en cas de réaction vaccinale typique (pustule).

A

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Appendix 4 Annexe 4

INTERNATIONAL CERTIFICATE OF VACCINATION OR REVACCINATION AGAINST SMALLPOX

CERTIFICAT INTERNATIONAL DE VACCINATION OU DE REVACCINATION CONTRE LA VARIOLE

This is to certify that / Je soussigné(e) certifie que) ..... date of birth / née le) ..... sex / sexe) .....

whose signature follows / dont la signature suit) .....

has on the date indicated been vaccinated or revaccinated against smallpox. / a été vacciné(e) ou revacciné(e) contre la variole à la date indiquée.

Date	Signature and professional status of vaccinator / Signature et qualité professionnelle du vaccinateur	Approved stamp / Cachet d'authentification		State whether primary vaccination or revaccination ; if primary, whether successful / Indiquer s'il s'agit d'une primovaccination ou de revaccination ; en cas de primovaccination, préciser s'il y a eu prise
1		1	2	
2				
3		3	4	
4				

The validity of this certificate shall extend for a period of three years, beginning eight days after the date of a successful primary vaccination or, in the event of a revaccination, on the date of that revaccination.

The approved stamp mentioned above must be in a form prescribed by the health administration of the territory in which the vaccination is performed.

Any amendment of this certificate, or erasure, or failure to complete any part of it, may render it invalid.

La validité de ce certificat couvre une période de trois ans commençant huit jours après la date de la primovaccination effectuée avec succès (prise) ou, dans le cas d'une revaccination, le jour de cette revaccination.

Le cachet d'authentification doit être conforme au modèle prescrit par l'administration sanitaire du territoire où la vaccination est effectuée.

Toute correction ou rature sur le certificat ou l'omission d'une quelconque des mentions qu'il comporte peut affecter sa validité.

B

Plate 7.12. **A:** The form proposed to the Fourth World Health Assembly in 1951, by the committee drafting the International Sanitary Regulations. **B:** The revised form approved by the Health Assembly.

haemagglutinin-inhibiting antibodies after revaccination as evidence of resistance to viral infection, these investigators found that such resistance increased with each successive 3-year revaccination, and suggested that the revaccination interval of health personnel at high risk could be prolonged beyond 3 years after 2 successful revaccinations. This result suggests that for international travellers the 3-year interval was conservative, but, as the WHO Committee on International Quarantine had concluded, it was administratively convenient, and continued to be accepted as long as vaccination certificates were required.

The day on which the certificate became valid after primary vaccination or revaccination was often debated at meetings of the WHO Committee on International Quarantine. The times agreed on in 1951—namely, 8 days after primary vaccination and the day after revaccination—were consistent with the earliest expected development of the immune response. Modifications, such as 12 or 14 days after the date of both primary vaccination and revaccination, were suggested, and the obligatory inspection of the vaccinial reaction was questioned. In a sense, this debate is a reflection on the ways in which international committees sometimes operate, especially in the absence of a real problem.

It is clear from these discussions that national health administrations attached considerable importance to the use of vaccination certificates, regarding them as one of the most important measures for preventing importations of smallpox. However, although all agree that because possession of a vaccination certificate was mandatory more travellers were vaccinated than would otherwise have been the case, the importance of this requirement is challenged by some critics, who point out that it was subject to abuse. For example, certificates were not always examined by the appropriate health officer at the point of entry, and if a passenger had transferred at an intermediate port in a smallpox-free country his vaccination certificate might not have

been examined at all. Worse, perhaps, were instances of deliberate falsification, or the provision of certificates by travel agencies to unvaccinated customers. Persons who had an apparently valid certificate might nevertheless contract smallpox if the vaccine or technique used had been faulty.

The situation was at its worst during the 1960s and 1970s, a period of greatly increased air travel, which reduced the travelling time between even the most distant endemic and non-endemic countries to a matter of hours. In earlier times, the inspection of all crew and passengers on ships from overseas ports to detect patients with smallpox had proved a useful method of limiting importations, especially into countries situated at some distance from endemic areas.

CHAPTER 8

THE INCIDENCE AND CONTROL OF SMALLPOX BETWEEN 1900 AND 1958

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INTRODUCTION

As has been described in Chapter 5, by the end of the 19th century variola major was endemic in most countries of the world and in every inhabited continent except Australia; and a new mild variety of smallpox, variola minor, was endemic in South Africa and the USA.

The present chapter explores the situation between 1900 and 1958 in greater detail than was given in the survey of the global incidence of smallpox in Chapter 4, drawing for the earlier data on Low (1918), Simmons et al. (1944–1954), Hopkins (1983a), various papers published in scientific journals, and records produced by national health authorities in several countries. It also traces in some detail the elimination of endemic smallpox in several countries in each continent in the years before 1958, which provided the rationale for the decision by the World Health Assembly to embark on a global smallpox eradication programme in 1959. Inevitably, because of the absence of reliable data from many countries and the inadequacy of the record even in those with the best data, the treatment of the subject is far from complete.

VARIATIONS IN THE INCIDENCE OF VARIOLA MAJOR AND VARIOLA MINOR

As Fig. 5.8 (Chapter 5) illustrates, the American strain of variola minor (alastrim) virus spread from the USA to Canada, South America, Europe, Australia and New Zealand. Viruses that differed from alastrim virus in several biological properties (see Chapter 2) caused variola minor in Africa, and their spread is more difficult to trace. African variola minor was endemic in southern Africa until 1973, and a similar disease was reported from time to time in many countries of eastern and central Africa, usually coexisting with endemic variola major. It is not clear whether its extension in Africa was due solely to spread from the southern African focus or whether there were other places in Africa in which a similar mutant form of the virus emerged, or indeed whether some outbreaks followed importations of alastrim from the homelands of the European colonial powers.

One of the most interesting epidemiological features of smallpox during the period 1920–1958 was the relation between variola major and variola minor in countries in which both varieties occurred. An important factor affecting their relative incidence was the attitude of the public at large and public health workers to smallpox control; in general, both were much more tolerant of variola minor than of variola major. This was evident in many countries—for example, Switzerland, in which variola minor was endemic between 1921 and 1926. When variola major occurred in Basle in 1921 (44 cases; 7 deaths) it was promptly controlled, whereas it took 6 years to eliminate variola minor from Switzerland (Sobernheim, 1929), leading to a pronouncement by the Swiss delegate to the 1926 International Sanitary Conference of the Office international d'Hygiène publique:

"[Smallpox] has, in reality, no place in an international convention. It is not a pestilential

disease in the proper sense of the term: it is, in effect, a disease that exists everywhere. There is probably not a single country of which it can be said that there are no cases of smallpox." (Cited by Howard-Jones, 1975.)

Three other factors were operative: the infectiousness of individual patients; the number of contacts with susceptible subjects; and the degree of protection afforded by vaccination, if it had been carried out many years earlier. Patients with variola major usually excreted more virus and were thus more infectious than patients with variola minor, and variola major was more likely to overcome the effects of slight residual immunity due to vaccination. On the other hand, the severity of systemic symptoms from the prodromal stage onwards was so great in variola major that most patients were confined to bed and thus their contacts were greatly limited. Patients with variola minor usually had such a mild systemic illness that they were often ambulant throughout the course of the disease, and therefore made many more close contacts.

These four factors, and the element of chance, in relation to viral mutation or importation, interacted to produce four patterns of endemicity:

(1) In very well vaccinated communities, such as in many countries of continental Europe in the 1930s, the level of immunity of the population was so high that variola minor could not become established. Any smallpox that did occur was variola major associated with importations.

(2) In countries such as the United Kingdom and the USA, with highly organized health services but without properly enforced compulsory vaccination, outbreaks of variola major were rapidly brought under control by isolation and selective vaccination, whereas variola minor evoked no such reaction from the health authorities. For example, in Detroit, Michigan, in 1923, at a time when variola minor was epidemic (710 cases in 6 months), the Health Department conducted vigorous propaganda for vaccination, but achieved only about 6000 vaccinations per month. Soon afterwards variola major was imported from Canada; the vaccination rate increased very greatly, half a million persons being vaccinated within 1 month and 800 000 (about 70% of the population) within 5 months.

(3) In populous countries in which vaccination was poor and the health services ineffective, such as India and Mexico, variola major predominated because of its greater capacity to infect and spread.

(4) In some African countries such as Ethiopia, in which at that time there was virtually no vaccination, endemic variola minor replaced variola major, probably during the 1950s. In this country of sparse population and very poor communications, the major factor favouring variola minor was probably its capacity to persist in small nomadic groups, among whom the transmission of variola major would have been interrupted spontaneously (see Chapters 4 and 21). Its persistence was probably helped by the widespread practice of variolation (see Chapter 21). For much of the period under review variola major and variola minor coexisted in many central, eastern and southern African countries.

Brazil does not fit readily into this classification. Although its health services were probably no better than those of Mexico during the 1920s and 1930s, alastrim replaced variola major in Brazil during the 1920s but never became endemic in Mexico.

THE ELIMINATION OF SMALLPOX FROM EUROPE BY 1953

One of the factors which led to the decision by the Twelfth World Health Assembly, in 1959, to adopt global eradication of smallpox as a major goal of the World Health Organization (see Chapter 9) was the fact that by this time eradication had been achieved in all the countries of Europe and of Central and North America. Tables 8.1 and 8.2 set out the incidence of reported cases of smallpox between 1920 and 1958, in selected countries of western and eastern Europe respectively.

The gradual elimination of endemic smallpox from the countries of Europe is illustrated in Fig. 8.1–8.3. In the following pages the overall position in Europe between 1900 and 1958 is described first, drawing on Low (1918) for data before the First World War. Stowman (1945), Fabre (1948), Murray (1951) and the *Epidemiological and vital statistics report* (1953) provide useful summaries of the incidence during both the First and the Second World Wars and the inter-war period. Following this summary, the situation in selected European countries for which more

Table 8.1. Western Europe: numbers of reported cases of smallpox in selected countries, 1920–1958[a]

	Germany[b]	United Kingdom	France	Italy[c]	Spain[c]	Belgium	Netherlands[c, d]	Austria	Portugal[c]	Switzerland
1920 population (millions)	62	44	39	37	21	8	7	6	6	4
1950 population (millions)	68	51	42	47	28	9	10	7	8	5
1920	2 115	1 007	392	26 453	*3 285*	91	50	253	*1 209*	2
1921	689	442	341	4 644	*2 097*	21	1	18	*267*	596
1922	215	980	172	534	*1 325*	23	0	4	*425*	1 153
1923	17	2 507	195	495	*525*	31	2	17	*660*	2 145
1924	16	3 801	210	432	*1 217*	31	3	1	*751*	1 234
1925	24	5 367	456	195	*849*	12	2	0	*468*	329
1926	7	10 147	565	112	*112*	13	15	0	*394*	54
1927	4	14 921	410	60	*162*	0	0	0	1 169	0
1928	5	12 560	153	*98*	*153*	1	0	0	923	1
1929	2	11 010	84	6	*2*	0	700	2	800	1
1930	2	11 853	217	2	49	0	2	0	815	1
1931	0	5 665	162	*4*	910	0	1	0	2 210	0
1932	3	2 359	134	2	1 066	0	0	0	4 246	2
1933	0	631	180	5	624	2	0	0	1 800	0
1934	0	184	199	*3*	688	0	0	0	1 016	0
1935	1	1	428	*1*	297	0	0	0	762	0
1936	0	12	312	2	114	0	0	0	836	0
1937	0	4	5	*1*	6	0	*1*	0	623	0
1938	0	19	2	0	19	0	0	0	706	0
1939	0	1	5	4	841	0	0	0	1 367	1
1940	0	2	5	0	1 874	0	0	0	880	0
1941	0	0	8	*1*	678	0	0	0	478	0
1942	1	124	63	*2*	371	0	0	0	431	0
1943	1	1	5	0	210	1	0	0	277	0
1944	0	16	4	2 878	128	0	2	0	332	0
1945	8	8	5	3 116	33	0	*3*	0	444	0
1946	2	55	10	772	44	0	*1*	1	895	0
1947	7	94	47	44	34	29	2	0	832	1
1948	3	0	3	9	23	1	0	0	334	0
1949	3	19	2	4	9	1	0	0	54	0
1950	0	28	1	1	2	0	0	0	65	0
1951	0	29	0	0	3	0	52	0	78	0
1952	0	135	75	0	3	0	0	0	34	0
1953	0	30	0	0	3	0	0	0	8	0
1954	0	0	15	0	2	0	40	0	0	0
1955	0	0	85	0	0	3	0	0	0	0
1956	0	0	0	0	0	0	0	0	0	0
1957	0	4	0	8	0	0	0	0	0	0
1958	6	6	0	0	0	0	0	0	0	0

[a] A horizontal line beneath a figure indicates that this represents the last probable occurrence of endemic smallpox.
[b] After 1945, consolidated figures for the German Democratic Republic and the Federal Republic of Germany.
[c] Figures in italics denote the number of reported deaths from smallpox.
[d] Endemic smallpox was eliminated before 1900, but importations occurred during most years up to 1926, and occasionally after that date.

Table 8.2. Eastern Europe: numbers of reported cases of smallpox in selected countries, 1920–1958[a,b]

	USSR	Poland	Czechoslovakia[c]	Yugoslavia	Romania	Hungary[c]	Bulgaria	Greece[c,d]	Finland[c]
1920 population (millions)	158	27	13	12	12	8	5	5	3
1950 population (millions)	180	25	12	16	16	9	7	8	4
1920	126 423	3 948	4 529	4 156	3 467	..	527	..	77
1921	100 004	5 078	1 642	2 119	2 744	131	22	*250*	27
1922	71 172	2 399	84	738	865	2	24	*292*	91
1923	47 678	502	36	1 042	89	9	20	2 101	12
1924	28 610	861	*33*	330	9	*11*	5	250	2
1925	18 548	77	*4*	14	28	*10*	0	16	2
1926	16 567	69	*8*	4	6	*2*	1	27	1
1927	14 164	36	*6*	7	4	*4*	2	102	0
1928	10 361	27	*7*	0	9	*1*	0	24	2
1929	6 413	20	*1*	0	4	0	0	7	1
1930	3 834	22	0	1	5	0	0	27	3
1931	9 471	14	*1*	0	13	2	0	12	5
1932	14 881	5	0	0	10	0	0	8	4
1933	2 160	6	0	0	6	0	0	9	2
1934	3 079	7	0	0	7	0	0	10	1
1935	3 167	4	0	0	0	0	0	9	2
1936	391	1	0	0	3	0	0	2	38
1937	11	2	0	0	15	0	0	3	2
1938	7	0	0	0	55	0	0	0	0
1939	0	0	*5*	0	0	0	4	0	0
1940	0	0	*19*	1	1	0	0	4	0
1941	0	..	*3*	0	0	0	0	0	*1*
1942	0	..	0	..	0	0	0	0	0
1943	0	..	*2*	..	0	0	0	831	0
1944	0	..	*1*	..	0	0	0	329	0
1945	0	0	*3*	..	0	0	0	0	0
1946	0	0	35	2	+	0	0	2	0
1947	0	0	0	0	0	0	0	0	0
1948	0	0	0	0	0	0	0	0	0
1949	0	0	0	0	0	0	0	0	0
1950	12	..	0	0	0	0	0	13	0
1951	305	..	0	0	0	0	0	0	0
1952	79	..	0	0	0	0	0	0	0
1953	0	..	0	0	0	0	0	0	0
1954	0	..	0	0	0	0	0	0	0
1955	70	0	0	0	0	0	0	0	0
1956	70	0	0	0	0	0	0	0	0
1957	1	0	0	0	0	0	0	0	0
1958	20	0	0	0	0	0	0	0	0

[a] A horizontal line beneath a figure indicates that this represents the last probable occurrence of endemic smallpox.
[b] .. = data not recorded; + = smallpox present, but number of cases unknown.
[c] Figures in italics denote the number of reported deaths from smallpox.
[d] Endemic smallpox was eliminated in 1934, but was re-established in 1943 and eliminated again in 1944.

Notes on the Statistical Tables

In order to illustrate the discussion presented in this chapter, a number of statistical tables are included to show the incidence of reported cases (rarely of reported deaths) in selected countries in various regions. The tables also show estimates of the populations of the countries listed near the beginning and end of the period for which the smallpox incidence is recorded, in order to give some indication of the sizes of the exposed populations. (The source of these population estimates is the United Nations *Demographic Yearbook, 1960* (United Nations, 1961) for the years 1920–1949 and *Population Prospects: Estimates and Projections as Assessed in 1982* (United Nations, 1985) for 1950 and subsequent years.)

Except in Portugal, Spain, the USSR and Mexico, most outbreaks of variola major in Europe and North America after about 1930 were due to importations and the numbers were reported reasonably accurately. However, experience in the Intensified Smallpox Eradication Programme showed that for countries of Africa, South America and Asia, the reported figures greatly underestimated the incidence, often representing no more than 1–2% of the true totals. In all countries in which variola minor was endemic, also, many cases were misdiagnosed or not reported. Nevertheless, the waxing and waning of the numbers of cases reported by various countries, as presented in these tables, reflect changes in the incidence of smallpox and provide evidence of its elimination from an increasing number of countries during the first half of the 20th century.

In each table the year considered by the authors to be the probable one in which endemic smallpox was eliminated from various countries is indicated by a horizontal line in the appropriate place; cases reported after this date are regarded as having been due to importations. As will be described in Chapter 23, such importations continued to occur in many countries until the mid-1970s. After endemic smallpox had been eliminated, outbreaks associated with importations rarely persisted for more than a few months.

It should be emphasized that just as the data on incidence given in the tables are often only an approximate indicator of the true incidence, it is also often impossible to determine in exactly which year smallpox ceased to be endemic in a particular country. After the Intensified Smallpox Eradication Programme had commenced operations, intensive surveillance made it possible to recognize the exact date of onset of the last case of endemic smallpox. In the period with which this chapter deals, however, smallpox sometimes just faded away; even the year in which the last endemic case occurred, let alone the precise date of its onset, is hard to determine. Where variola minor was prevalent, as in the USA, "smallpox" continued to be reported on the basis of faulty diagnoses after it had ceased to be endemic. The dates given for the elimination of endemic smallpox before 1958 are therefore sometimes a matter of judgement rather than of precise knowledge.

detailed data are available is described at greater length. The same procedure is used for the other continents.

The latter part of the 19th century had seen a great decline in smallpox in most countries of Europe, as glycerolated calf-derived vaccine became available, health services improved and vaccination and revaccination were practised more extensively (see Chapter 6). The decline continued during the early years of the 20th century, the incidence of smallpox being particularly low in the well-vaccinated populations of Austria, Germany and the Scandinavian countries. In contrast, the Iberian peninsula continued to suffer from endemic smallpox with periodic severe outbreaks.

Low (1918) has summarized published information on the world-wide incidence of smallpox during the period before any international statistical organization existed; his report provides an invaluable source of data for the early part of the 20th century. Table 8.3 summarizes some of Low's figures on the

numbers of reported deaths from smallpox in various countries of Europe between 1900 and 1914. Because of the persistently high incidence of smallpox in Russia, travellers from that country were a particularly important source of importations of smallpox into its European neighbours, especially the Scandinavian countries and Germany. Fortunately, in view of the strong antivaccinationist movement prevailing there at that time, the British Isles were shielded to some extent from importations from mainland Europe, because of the small number of travellers from Russia. Importations from the colonies were also infrequent, because the long voyage by ship ensured that infected persons who had embarked during the incubation period became ill before arrival and could therefore be recognized and isolated. The last large outbreaks of variola major in the United Kingdom occurred in 1902–1903.

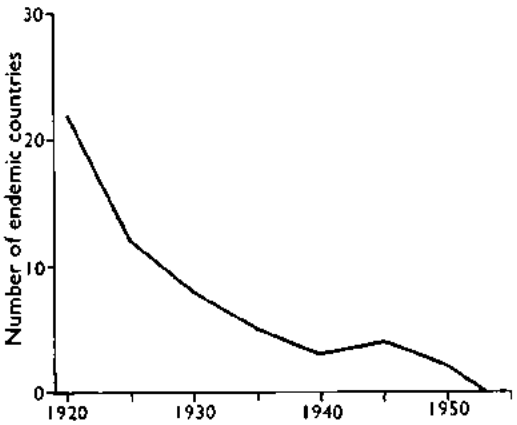

Fig. 8.1. Number of countries in Europe in which smallpox was endemic at various times between 1920 and its continental elimination in 1953 based on the 30 political divisions operative in 1982—i.e., those shown in Fig. 8.2 together with Cyprus, Malta and Luxembourg (all non-endemic) and Turkey (see Fig. 8.11).

The disruption and mass movements associated with the First World War exacerbated the disease in Russia—it was particularly severe in Russian Poland—and from Russia it spread to Germany, Austria and Sweden. Smallpox remained endemic in Italy, Romania and Yugoslavia, and in the area that later formed the new state of Czechoslovakia, as well as in Portugal and Spain. In the aftermath of the First World War the situation became even worse. During 1918–1920 severe epidemics killed 28 000 persons in Italy, 14 000 in Portugal and 1500 in Germany; in the USSR 186 000 cases were

Table 8.3. Europe: numbers of reported deaths from smallpox in selected countries, 1900–1919, by quinquennium[a,b]

Country	1910 population (millions)	Number of deaths from smallpox			
		1900–1904	1905–1909	1910–1914	1915–1919
Russia	134	218 000[c]	221 000[c]	200 000[c]	535 000 [cases][c,d]
Germany	65	165	231	136	1 323
France	39	8 448	3 860	825	576
England and Wales	36	4 174	180	65	64
Italy	34	18 590	2 149	8 773	17 453
Austria	28	547	127	350 [cases][d]	52 286 [cases][d]
Hungary	20	2 672	1 057	284[e]	..
Spain	20	24 895	17 083	11 660	13 037
Belgium	7.5	3 391	422	..	..
Romania	7.0	37	3	38	..
Portugal	5.9	2 789[f]	10 510	1 724[g]	15 141
Netherlands	5.8	51	28	6	9
Sweden	5.5	6	4	3	29
Scotland	4.5	637	12	23	3
Ireland	4.4	60	6	0	0
Switzerland	3.7	75	62	16	0
Finland	3.0	295	155	182	1 605
Denmark	2.8	7	4	3	0
Norway	2.3	0	27	2	2

[a] Based on Low (1918) and Henneberg (1956).
[b] .. = no data recorded.
[c] Approximate.
[d] Number of reported cases.
[e] Up to 1912 only.
[f] Refers to 1902, 1903 and 1904 only.
[g] Refers to 1910, 1913 and 1914 only.

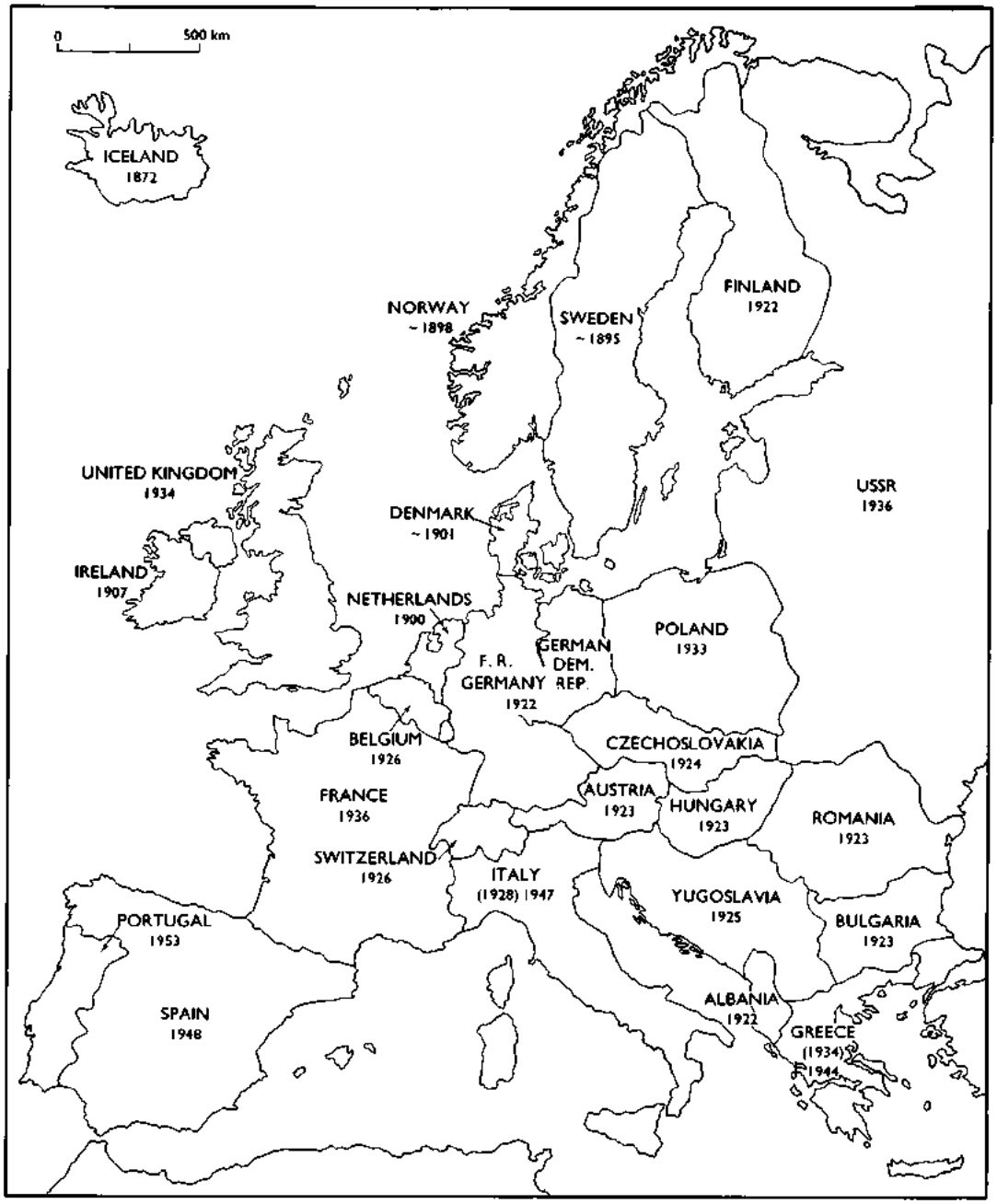

Fig. 8.2. Europe: year in which smallpox ceased to be endemic in each country (national boundaries as of 1982). Dates in parentheses (for Greece and Italy) indicate the initial elimination of endemic smallpox, after which endemicity was again established before final elimination in the year shown.

reported in 1919. For political reasons, Switzerland had sealed its borders throughout the First World War and this saved it from imported smallpox, which had been a major problem in the Franco-Prussian War of 1870–1871.

As countries recovered from the ravages of the war and as effective public health measures were reinstated, variola major became much less common. However, in the early 1920s alastrim was imported into the United Kingdom from the USA and became estab-

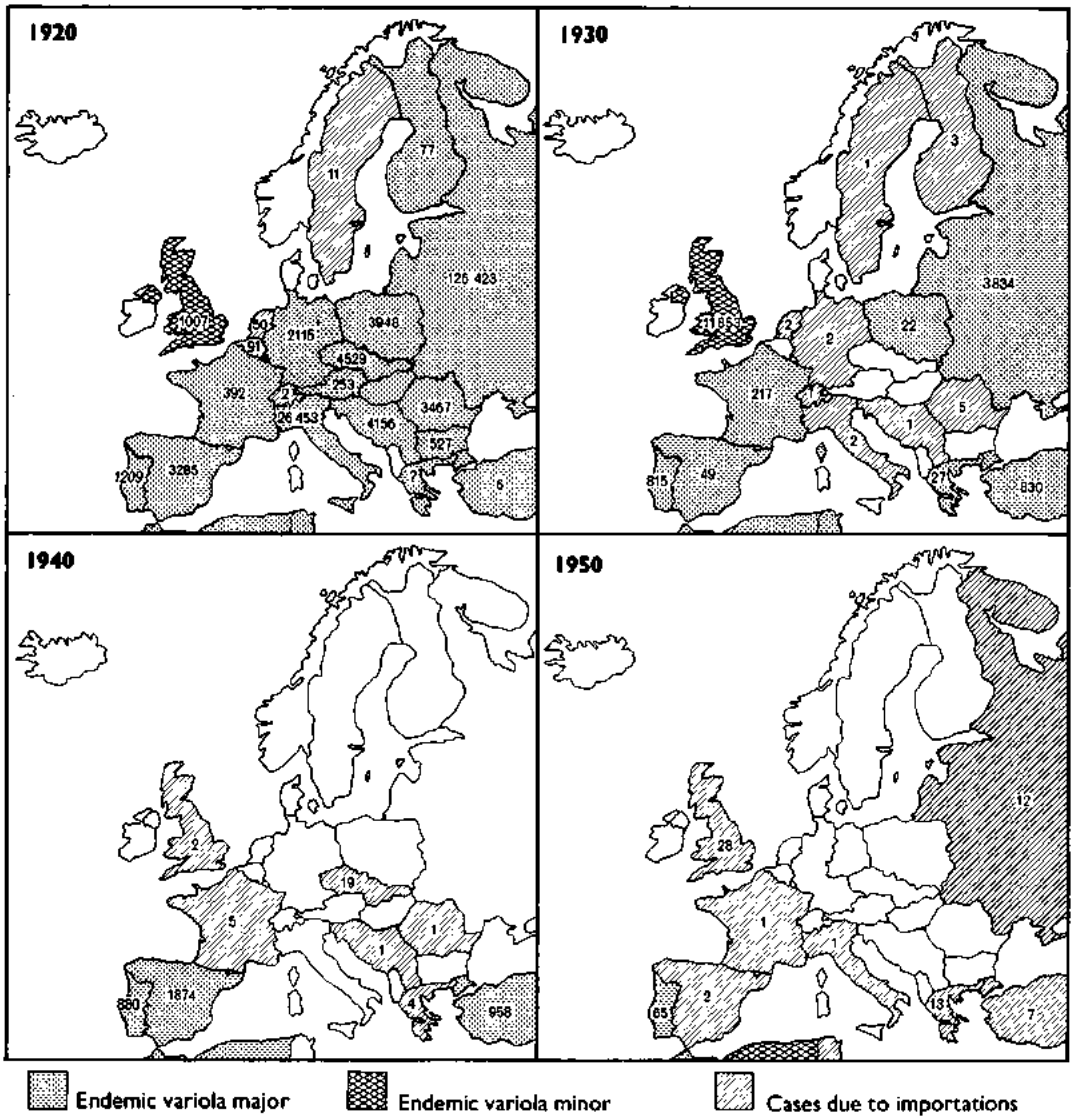

Fig. 8.3. Europe: countries with endemic variola major, endemic variola minor or with importations, and the number of reported cases of smallpox for the years 1920, 1930, 1940 and 1950. (Based on Jezek et al., 1982.)

lished there as an endemic disease, producing over 10 000 reported cases each year between 1926 and 1930. It was finally eliminated in 1934. It occurred in a few other European countries: "... in 1922 the mild non-fatal type was the rule in Finland, Germany, Switzerland, Egypt, Cuba, Jamaica, South Africa and parts of Canada and the United States, as well as the United Kingdom (England and Wales, Ministry of Health, 1923). Alastrim broke out in the Netherlands in 1929, and it occurred concurrently with variola major in Spain and Portugal in 1936. However, the only other prolonged outbreak of variola minor in Europe was in Switzerland, in which over 5000 cases occurred between 1921 and 1926.

By the late 1930s endemic smallpox had been eliminated from most countries of Europe except Portugal, Spain (which experienced a resurgence after the Spanish Civil War, with over 1500 deaths in 1939–1940) and Turkey.

In contrast to the severe and widespread epidemics of smallpox in Europe after the First World War, only isolated incidents occurred during and after the Second World

War. Variola minor was imported into Italy from North Africa in 1944 and produced over 6000 reported cases before it was eliminated in 1947, while variola major occurred in Turkey during the war (over 12 000 reported cases in 1943; see Table 8.18) and extended from there to Greece.

From 1953 onwards Europe was free of endemic smallpox, but countries with colonial possessions in tropical regions—France, Portugal, the United Kingdom, and to some extent Belgium and the Netherlands—were especially liable to importations, rapid aerial transit of infected persons from endemic regions to Europe greatly increasing the hazard. Small outbreaks, often largely hospital-associated, occurred in all these countries (see Chapter 23).

United Kingdom

Statistical data for the United Kingdom are provided separately for England and Wales, Scotland and Northern Ireland. Endemic smallpox was eliminated from Ireland in 1907 and subsequent importations were rare and quickly contained. Variola major was prevalent in Scotland from 1900 to 1905, with 6628 cases and 641 deaths, over half the cases occurring in Glasgow. From then on in only one outbreak did the number of cases exceed 80, but there were importations into the east coast ports from northern Europe and into Glasgow from Spain and the USA. Some cases of variola minor occurred in Scotland in 1927–1930 (maximum numbers reported: 154 in 1927 and 146 in 1928) as an extension of the much greater prevalence of the disease in England at that time. However, as is not surprising in view of the relative sizes of the populations of the constituent parts of the United Kingdom, the major brunt of smallpox was borne by England and the data for England and Wales are therefore discussed separately, and in greater detail, below.

England and Wales

Variola major. The last large epidemic of variola major in London occurred in 1901–1902, with 9496 reported cases and 1543 deaths, and there was an outbreak in Liverpool in 1902–1903, with 2280 reported cases and 161 deaths. Importations of variola major continued to cause small outbreaks in most years until about 1929, after which they became fewer and were more rapidly controlled. The years 1939–1945 were characterized by an almost complete absence of smallpox, but there was an upsurge in 1946 and 1947, with many small outbreaks (Table 8.4). Variola major continued to be imported into England more frequently than into any other country of Europe for the whole of the period under review. The overall annual figures given in Table 8.4 do not accurately reflect the frequency of these importations. In 1946, for example, as British soldiers were being repatriated from distant parts of the world and with the post-war entry of students from Africa and Asia, no fewer than 15 separate introductions accounted for the 56 cases reported.

There were two reasons for the frequency with which smallpox was imported into the United Kingdom. The first was the extensive movement to and from endemic areas in Africa and Asia, associated with the country's imperial role and the traditions of movement that remained in the post-colonial period. The second was the fact, trenchantly criticized in the medical press (see, for example, *British medical journal*, 1962), that alone of the advanced industrial nations the United Kingdom had no requirement that overseas travellers should carry a valid international vaccination certificate. The latter situation was changed in 1963, when all persons seeking entry to the United Kingdom from an infected local area—in no matter what country—and from all countries of Africa, the Americas (except Canada and the USA) and Asia were required to produce a valid international certificate of vaccination. Especially in the period just after the Second World War, many of the importations were due to mild attacks of modified-type variola major in vaccinated servicemen (Murray, 1951). The low community acceptance of vaccination in infancy, even when it had been nominally compulsory (up to 1946), and the failure to vaccinate hospital workers regularly allowed such cases to infect others (especially hospital personnel) and thus to initiate outbreaks.

Variola minor. There were apparently a few small outbreaks of variola minor in England early in the 20th century (*Lancet*, 1903), one in Nottingham in 1901 being attributed to contaminated fomites sent from Salt Lake City, USA, to a Mormon convention (Boobbyer, 1901), after which it spread to several other cities and then apparently died out.

Table 8.4. England and Wales: numbers of reported cases of and deaths from variola major and variola minor, 1911–1958[a]

Year	Variola major			Variola minor		
	Number of cases	Number of deaths	Case-fatality rate (%)	Number of cases	Number of deaths	Case-fatality rate (%)
1911	295	23	8	0	–	–
1912	123	9	7	0	–	–
1913	115	10	9	0	–	–
1914	64	4	6	0	–	–
1915	90	13	14	0	–	–
1916	149	16	11	0	–	–
1917	7	3	42	0	–	–
1918	63	2	3	0	–	–
1919	294	24	8	36	0	–
1920	180	30	17	83	0	–
1921	45	5	11	277	0	–
1922	78	24	31	895	3	0.3
1923	18	2	11	2 467	5	0.2
1924	0	–	–	3 765	13	0.3
1925	10	1	10	5 365	9	0.2
1926	5	1	20	10 141	17	0.2
1927	17	7	41	14 753	40	0.3
1928	0	–	–	12 420	53	0.4
1929	42	14	30	10 925	25	0.3
1930	0	–	–	11 839	28	0.2
1931	0	–	–	5 664	9	0.2
1932	0	–	–	2 039	3	0.1
1933	0	–	–	631	2	0.3
1934	26	4	15	153	2	1.3
1935	0	–	–	0	–	–
1936	12	0	–	0	–	–
1937	3	?	?	0	–	–
1938	7	3	43	0	–	–
1939	0	–	–	0	–	–
1940	0	–	–	0	–	–
1941	0	–	–	0	–	–
1942	2	0	–	0	–	–
1943	0	–	–	0	–	–
1944	11	3	27	0	–	–
1945	4	–	–	0	–	–
1946	56	14	25	0	–	–
1947	78	15	19	0	–	–
1948	0	–	–	0	–	–
1949	19	5	26	0	–	–
1950	8	0	–	0	–	–
1951	27	10	37	0	–	–
1952	0	–	–	135	0	–
1953	29	8	27	0	–	–
1954	0	–	–	0	–	–
1955	0	–	–	0	–	–
1956	0	–	–	0	–	–
1957	7	3	43	0	–	–
1958	5	1	20	0	–	–

[a] Based on Dixon (1962). Differences for some years from the numbers given in Table 8.1 are due to the use of different sources.

Interestingly, the only 2 importations of variola minor into Oceania—separate episodes in Australia and New Zealand in 1913—were attributed to Mormon visitors. Variola minor first appears to have become well established in England in 1919 (Copeman, 1920). Once again, it is difficult to trace its first occurrence, since it was often confused with chickenpox, but initially it seems to have been commonest in the north of England, with small pockets in the south. London was first affected in 1928.

Table 8.4 illustrates the remarkable difference in the incidence of variola major and variola minor in England and Wales during the period between the wars. Variola major was eliminated as an endemic disease early in the century, but subsequently often occurred as small outbreaks resulting from importations, which were always rapidly controlled. There were 35 such circumscribed outbreaks, with a total of 268 cases, in 14 out of the 24 years between 1935 and 1958. On the other hand, variola minor was a common endemic

disease from 1919 until 1934. When importations of variola minor did subsequently occur, as in 1952 and 1966 (the latter probably laboratory-associated; see Chapter 23), they caused many more cases (135 and 72 respectively) than did the outbreaks of variola major, the largest of which, in 1947, produced 48 cases before being brought under control.

Unquestionably, in the United Kingdom, as in the USA at about this time, the health authorities took variola major seriously and reacted effectively, with surveillance, the isolation of cases and the vaccination of contacts, but they paid relatively little attention to variola minor. It is perhaps not surprising that in the 1970s WHO officials experienced great difficulty in persuading the health authorities in Ethiopia to look upon variola minor as a disease of sufficient importance to make a call on their limited resources (see Chapter 21).

Russia and the Union of Soviet Socialist Republics

Smallpox ravaged European Russia during the early part of the 20th century and was even worse during the misery that accompanied and followed the First World War. Russia was feared by its neighbours as a source of smallpox; ships from Russian ports were a recognized hazard in Scandinavia and most of the cases of smallpox in Germany were in areas near the eastern borders. Indeed in 1910 almost 30% of all cases of smallpox reported in Germany occurred in travellers from Russia (Jones, 1914).

With the establishment of the USSR in 1917, the new government took steps to control smallpox, and vaccination was made mandatory in a decree signed by V. I. Lenin in April 1919. In 1924, the Soviet vaccination law was modified to require vaccination in infancy and the revaccination of teenagers (Kravchenko, 1970). Nevertheless, smallpox continued, with severe epidemics in European Russia in 1931–1933 that led to intensified vaccination campaigns and the elimination of endemic smallpox in 1936 (Vasil'ev & Vasil'ev, 1982). Subsequently, outbreaks following importations were reported in 1950–1952, 1955, 1956 and 1958 (see Table 8.2). The last outbreak occurred in 1960, when an importation from India caused 46 reported cases and 3 deaths in Moscow (Barojan & Serenko, 1961; see Chapter 23).

Germany

The German states had been among the first in Europe to adopt compulsory vaccination and revaccination and the comparative freedom of the Prussian armies from smallpox in the Franco-Prussian War of 1870–1871 testified to the effectiveness of these measures (see Chapter 6). By 1900 vaccination of the civilian population had reached a high level and variola major had ceased to be endemic. However, for economic reasons large numbers of foreign agricultural workers and skilled tradesmen were recruited from Russia, in which vaccination was poor and variola major still common. In consequence, there were many small outbreaks initiated by imported cases.

In the aftermath of the First World War there were outbreaks totalling several thousand cases between 1916 and 1922, when endemic smallpox was again eliminated. In spite of the devastation, there was almost no smallpox in Germany during and immediately after the Second World War, but importations, with limited spread, occurred in 18 of the 36 years between 1922 and 1958.

France

During the early years of the 20th century smallpox was much commoner in France than it was in Germany. Vaccination in infancy was made compulsory in 1902, with provision for revaccination at 11 and again at 21 years of age, but the law was not enforced. Paris and Marseilles were the principal centres of infection, especially Marseilles, the main port of entry for passengers and merchandise from endemic countries of North Africa and western Asia. One noteworthy advance was in the French army, in which smallpox had been so severe during the Franco-Prussian War. From 1914 to 1917 the army did not report a single case of smallpox.

A few hundred cases were notified almost annually between 1920 and 1936, and minor outbreaks associated with importations occurred in most of the following years (see Table 8.1). There was little smallpox in France during the Second World War, but subsequently local outbreaks occurred almost every year until 1956, though they were usually quickly contained. Many were very mild, the original cases usually being diagnosed as chickenpox (Fabre, 1948).

Portugal and Spain

During the first quarter of the 20th century Portugal, for long one of the most economically depressed countries of Europe, sustained endemic variola major at a level rivalling that of countries in Africa and Asia at that time (Amaral, 1960). Its larger neighbour, Spain, was not much better off, although the incidence was briefly reduced twice (in 1929 and again in 1937) only to rise again, notably in the aftermath of the Spanish Civil War. Classical variola major occurred throughout this period, but from 1944 to 1948 the overall case-fatality rate was only 3.1% and the reports indicated that both variola major and variola minor were present. Only variola minor occurred after that, until endemic smallpox was eliminated from both countries by the early 1950s.

Scandinavia

Smallpox had been a severe disease in Sweden during the latter half of the 18th century, killing an estimated 10% of the population (see Chapter 6, Fig. 6.1). Compulsory vaccination was introduced in 1816 and greatly reduced the incidence but endemic smallpox was not eliminated until the end of the 19th century. There were small outbreaks almost every year during the first two decades of the 20th century (Table 8.5), due to importations. In 1917 a substantial outbreak occurred, associated with the passage of war invalids from Russia to Germany, but after 1920 there were cases in only 9 of the 43 years up to 1963, when an outbreak of variola major with 27 cases occurred, which was reported in great detail (Ström & Zetterberg, 1966).

Denmark and Norway, smaller countries with less international trade and travel than Sweden, also remained free of endemic smallpox for the whole of the 20th century, but both countries occasionally reported single cases or very small outbreaks associated with importations.

The Scandinavian countries provided an example for the rest of the world. Subject to severe endemic and epidemic smallpox before vaccination became available, they eliminated smallpox by the end of the 19th century, and for the most part successfully excluded importations thereafter. When importations did occur, they were usually rapidly controlled.

Table 8.5. Sweden: status of smallpox, 1900–1962[a]

Period	Number of outbreaks	Number of cases	Number of deaths
1900–1904	10	89	2
1905–1909	6	55	1
1910–1914	5	51	3
1915–1919	8	244	23
1920–1924	3	14	3
1925–1929	0	0	0
1930–1934	1	13	1
1935–1962	0	–	–

[a] Based on Zetterberg et al. (1966).

THE ELIMINATION OF SMALLPOX FROM NORTH AMERICA, CENTRAL AMERICA AND PANAMA BY 1951

The incidence of reported cases of smallpox in the USA, Mexico and Canada from 1920 to 1952 is shown in Table 8.6, and in the countries of Central America and Panama in Table 8.7. Two patterns are apparent in North America. The high incidence of smallpox in the USA from the beginning of the century was due mainly to variola minor with occasional outbreaks of variola major due to importations, and the situation was similar, on a smaller scale, in Canada. In Mexico, however, variola major occurred as a widespread disease from the beginning of the century, as it had during previous centuries (see Chapter 5). Variola minor was periodically introduced into Mexico from the USA but seems never to have become established there. Endemic smallpox was eliminated from all 3 countries by 1952.

Central America and Panama

Early records are sparse for the 7 small states constituting Central America and Panama, located between Mexico in the north and Colombia in the south (see Fig. 8.6), but variola major appears to have been present in most of them during the early years of the 20th century (Low, 1918). However, from 1920 onwards most of these countries were free of endemic smallpox, although there were importations and outbreaks extending over several years in the more populous countries until the mid-1950s (Table 8.7).

Table 8.6. North America: numbers of reported cases of smallpox, 1920–1952[a,b,c]

	United States of America	Mexico[d]	Canada
1920 population (millions)	106	14	9
1950 population (millions)	152	27	14
1920	110 672	..	..
1921	108 487	..	..
1922	33 305	*11 966*	..
1923	30 890	*13 074*	..
1924	56 513	*12 964*	2 791
1925	39 381	*11 008*	1 248
1926	32 694	*5 477*	1 535
1927	37 977	*6 639*	2 845
1928	39 396	*8 794*	3 337
1929	42 341	*11 304*	1 952
1930	48 329	*17 405*	1 292
1931	30 151	*15 003*	865
1932	11 194	*8 456*	347
1933	6 491	*6 094*	100
1934	5 371	*9 430*	17
1935	7 957	*5 205*	34
1936	7 834	*4 651*	62
1937	11 673	*3 538*	59
1938	14 939	*3 343*	120
1939	9 877	*2 205*	198
1940	2 795	*1 341*	11
1941	1 396	*2 529*	26
1942	865	*4 115*	6
1943	765	*4 011*	6
1944	398	3 516	0
1945	346	1 718	5
1946	357	600	2
1947	176	1 123	0
1948	57	1 541	0
1949	49	1 030	0
1950	0	769	0
1951	0	27	0
1952	0	0	0

[a] No cases were reported from any of these countries after 1951, except for 1 imported case in Canada in 1962.
[b] A horizontal line beneath a figure indicates that this represents the last probable occurrence of endemic smallpox.
[c] .. = data not recorded.
[d] Only deaths (figures in italics) were reported between 1922 and 1943.

United States of America

The history of smallpox in the USA in the period under review is dominated by the appearance of variola minor in Florida in about 1896 and its subsequent spread throughout the country and into Canada. This has been discussed at length by Chapin (1913, 1926) and Chapin & Smith (1932); the decline of smallpox after 1930 has been described by Dauer (1940). Table 8.8 sets out the numbers of reported cases of and deaths from smallpox from 1900 until the last cases occurred in 1949. The subdivision of annual totals of cases and deaths into variola major and variola minor derives in the main from Chapin & Smith (1932), who explored many sources in order to make their judgements about the variety of smallpox ("mild" or "severe") responsible for various outbreaks.

Variola major prevailed throughout the USA until the summer of 1897 but by then had disappeared from the country except for about 100 cases, with 30 deaths, which occurred in 16 different states. These local outbreaks were efficiently controlled and endemic smallpox appeared to have been eliminated (Chapin, 1913). However, during the first half of 1897 there were 54 cases of smallpox in Pensacola, Florida, and many more in the county in which Pensacola is situated, without a single death. From here the mild variety of smallpox, variola minor, spread through Florida, and in the year ending 31 March 1898, 3638 cases were reported, with only 51 deaths (case-fatality rate, 1.4%). Within a period of 4 years variola minor extended gradually over the whole of the continent north of the Mexican border (Fig. 8.4).

Table 8.7. Central America (excluding Belize) and Panama: numbers of reported cases of smallpox, 1920–1958[a,b,c]

	Guatemala	El Salvador	Honduras	Nicaragua	Costa Rica	Panama
1920 population (millions)	1.3	1.2	0.9 (1926)	0.7 (1933)	0.4	0.4
1950 population (millions)	3.0	1.9	1.4	1.1	0.9	0.9
1920	..	..	..	..	..	25
1921	..	..	..	..	..	215
1922	..	..	..	..	..	14
1923	..	..	..	..	..	0
1924	..	..	..	..	..	0
1925	..	0	..	..	0	0
1926	..	0	0	..	0	0
1927	*96*	0	0	..	0	0
1928	..	0	0	..	5	2
1929	..	0	0	..	0	396
1930	*10*	0	0	..	36	0
1931	*29*	*6*	0	..	0	2
1932	*23*	*18*	124	..	0	0
1933	*9*	*37*	38	..	2	0
1934	*38*	..	15	..	1	0
1935	*40*	484	8	..	0	0
1936	52	246	..	..	0	0
1937	*21*	10	..	1	1	4
1938	60	19	3	6	0	0
1939	11	*3*	3	4	1	0
1940	8	1	..	43	0	0
1941	6	0	6	5	1	15
1942	1	*1*	0	0	1	2
1943	6	*1*	2	6	0	1
1944	9	*1*	9	1	0	2
1945	5	*1*	8	148	1	0
1946	9	*1*	1	6	0	0
1947	11	0	0	1	9	12
1948	*12*	0	0	0	1	0
1949	*10*	0	0	0	0	0
1950	10	0	82	5	0	0
1951	3	0	105	6	0	0
1952	1	0	23	0	0	0
1953	4	0	0	18	0	0
1954	0	0	0	6	0	0
1955	0	0	0	3	0	0
1956	0	0	0	0	0	0
1957	0	0	0	0	0	0
1958	0	0	0	0	0	8

[a] A horizontal line beneath a figure indicates that this represents the last probable occurrence of endemic smallpox.
[b] .. = data not recorded.
[c] Figures in italics denote the number of reported deaths from smallpox.

The substrain of variola minor that was later called "alastrim" (see Chapter 2) remained the dominant form of smallpox in the USA thereafter. The number of cases notified each year represents at most 20% of those that actually occurred; many patients did not see a physician and many others who did were not reported as having smallpox. From the USA alastrim was exported to the United Kingdom (in 1902 and again in 1919), and to Brazil (1910), Australia (1913), New Zealand (1913) and the Philippines (about 1920). Against the background of endemic alastrim, repeated introductions of variola major occurred, mostly from Mexico (14 out of 23 outbreaks between 1915 and 1929) but also from Canada and overseas countries, especially Europe, during the early years of the century.

Chapin & Smith (1932) examined the detailed reports of as many outbreaks of variola major (the "severe type" of smallpox) as they could, in order to determine whether variola minor (the "mild type") ever gave rise to variola major. Their conclusion was that each variety of smallpox was due to a different subspecies of variola virus and that these "bred true". Subsequent experience in many parts of the world has confirmed this conclusion.

Although some cases of variola major were reported every year from 1900 until 1927, there were only 2 major outbreaks during this period. The first, in 1902–1903, affected particularly Boston, New York, Philadelphia, New Jersey and Ohio; variola minor was then prevalent in the Mid-West. The last large

Table 8.8. United States of America: numbers of reported cases of and deaths from variola major and variola minor, 1900–1950[a]

Year	Variola major			Variola minor		
	Number of cases	Number of deaths	Case-fatality rate (%)	Number of cases	Number of deaths	Case-fatality rate (%)
1900	3 328	603	18.1	17 736	291	1.6
1901	5 332	980	18.4	57 042	396	0.7
1902	10 334	1 841	17.8	62 612	669	1.1
1903	6 113	752	12.3	46 624	828	1.8
1904	5 539	866	15.6	26 158	416	1.6
1905	1 798	272	15.1	17 619	134	0.8
1906	669	44	6.6	14 554	46	0.3
1907	359	23	6.4	18 618	73	0.4
1908	391	27	6.9	33 607	81	0.2
1909	193	36	18.7	23 367	119	0.5
1910	1 216	252	20.1	30 038	177	0.6
1911	359	76	21.2	22 685	98	0.4
1912	1 164	204	17.5	22 402	101	0.5
1913	354	98	27.7	38 046	161	0.4
1914	195	66	33.8	40 279	150	0.4
1915	578	177	20.2	37 803	130	0.3
1916	300	78	26.0	19 440	169	0.9
1917	973	174	17.9	46 535	146	0.3
1918	311	63	20.3	80 023	351	0.4
1919	1 121	172	15.3	61 755	155	0.3
1920	1 214	157	12.9	109 458	291	0.3
1921	3 152	320	10.2	105 335	438	0.4
1922	2 650	643	24.3	30 655	258	0.8
1923	301	65	21.6	30 589	100	0.3
1924	4 782	633	13.2	51 731	263	0.5
1925	2 633	536	20.4	36 748	188	0.5
1926	1 560	238	15.1	31 134	152	0.5
1927	0	–	–	37 977	151	0.4
1928	0	–	–	39 396	141	0.4
1929	59	11	18.6	42 282	145	0.3
1930	0	–	–	48 329	170	0.4
1931	0	–	–	30 151	104	0.3
1932	0	–	–	11 194	52	0.5
1933	0	–	–	6 491	35	0.5
1934	0	–	–	5 371	21	0.4
1935	0	–	–	7 957	23	0.3
1936	0	–	–	7 834	33	0.4
1937	0	–	–	11 673	30	0.3
1938	0	–	–	14 939	46	0.3
1939	0	–	–	9 877	39	0.4
1940	0	–	–	2 795	15	0.5
1941	0	–	–	1 396	12	0.9
1942	0	–	–	865	3	0.3
1943	0	–	–	765	6	0.8

	Smallpox (variety not determined)		
	Number of cases	Number of deaths	Case-fatality rate (%)
1944	398	9	2.3
1945	346	12	3.5
1946	357	24	6.7
1947	176	?	?
1948	57	?	?
1949	49[b]	1	2.0
1950	0	–	–

[a] Based on Chapin & Smith (1932) and relevant issues of *Public health reports*.
[b] The last probable occurrence of endemic smallpox.

epidemic of variola major in the USA occurred in 1924–1925, when some 7400 cases were reported, over one-third of them in 4 cities: Cleveland and Toledo (Ohio), Detroit (Michigan) and Pittsburgh (Pennsylvania).

Vaccination played an important role in both the progressive fall in the incidence of smallpox and in the replacement of variola major by variola minor. The virtual disappearance of variola major and the mild nature

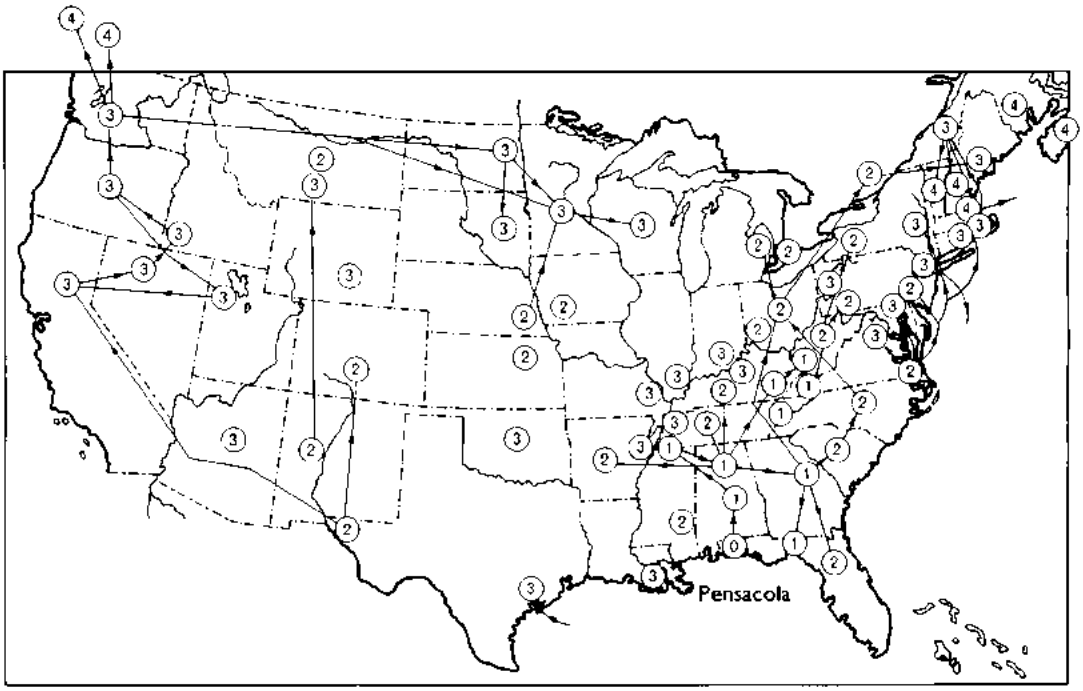

Fig 8.4. The spread of variola minor in the USA. It was first observed in Pensacola, Florida, in 1896. Figures in circles indicate the number of years elapsed between 1896 and the detection of cases in various cities in the USA including Alaska and in Canada. Arrows indicate directions of spread, when this could be determined, except for towns along the Mississippi, where the river was the route of spread. (Based on Chapin, 1913.)

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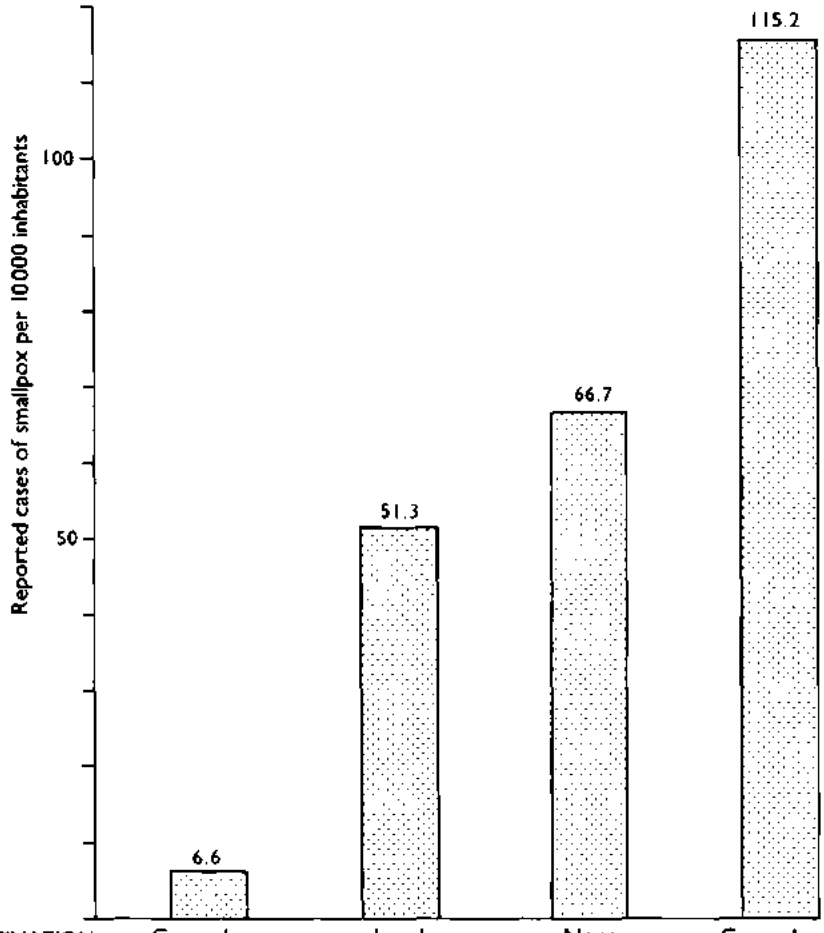
Plate 8.1. Charles Value Chapin (1856–1941) was Superintendent of Health of Providence, Rhode Island (USA), from 1884 to 1932. A nationally renowned figure, he imaginatively translated newly emerging concepts of the epidemiology of infectious diseases and methods for their prevention into public health administrative practice.

of variola minor led to the emergence of antivaccinationist sentiments, although in 1922 the United States Supreme Court had ruled that school authorities had the right to require vaccination for admission to school (Vaughan, 1923). By the 1930s, 4 states of the USA had laws prohibiting compulsory vaccination, 28 states had no vaccination laws, 6 provided for local option and 10 had compulsory vaccination laws. The relation between the legal situation and the incidence of variola minor is illustrated in Fig. 8.5.

In the year 1927, for the first time, no case of variola major was reported in the USA, and apart from an outbreak in 1929 no further cases were notified until 1946. In that year a soldier returning from Japan introduced smallpox into Seattle, Washington, which resulted in an outbreak of 51 cases, with 16 deaths (Palmquist, 1947). In 1947 a man with undiagnosed haemorrhagic smallpox died in a Manhattan, New York, hospital. Twelve other persons were infected and in the panic occasioned by this outbreak over 6 million



VACCINATION LAWS	Compulsory	Local option	None	Compulsory vaccination prohibited
NUMBER OF STATES	10	6	28	4
POPULATION	32 434 954	17 930 882	59 923 117	4 002 888
CASES OF SMALLPOX	21 543	91 981	393 924	46 110

Fig. 8.5. The effect of vaccination laws on the incidence of smallpox in various states of the USA, 1919 – 1928. (Based on Woodward & Feemster, 1933.)

New Yorkers were vaccinated (Weinstein, 1947). The last outbreak of smallpox in the USA occurred in Texas in 1949 (8 cases with 1 death), probably after importation from Mexico.

Although variola major was eliminated as an endemic disease in 1927, variola minor continued to be common in states without compulsory vaccination laws. Reporting methods changed in 1944, and it is impossible to get an accurate picture of the elimination of variola minor from the USA. Although grossly underreported when it was common, it was probably incorrectly diagnosed and reported during the few years just before and after its elimination from the USA, during the latter half of the 1940s.

Canada

The situation in Canada reflected that in the USA, with variola minor as the commonest form of smallpox after it became established there early in the century. However,

control by vaccination was more easily achieved in this less populous country and endemic smallpox was eliminated by 1944.

Mexico

The situation in Mexico in the earlier part of the 20th century contrasted starkly with that in Canada and the USA. Mexico had a population of about 14 million in 1920 and between 5000 and 13 000 smallpox deaths were reported every year in the 1920s (see Table 8.6), at that time the highest reported incidence in any country in the world (Hedrich, 1936). Variola minor appeared in Mexico in 1932, probably after importation from the USA, but it did not displace variola major, which caused a major epidemic with over 8000 deaths in 1942–1943. This led to an increased emphasis on vaccination, which became possible in many rural areas because of the development of roads. There was a rapid fall in the number of reported cases of smallpox, which continued to be of the variola major variety, and a change was made in reporting, from "deaths" to "cases" (see Table 8.6). The last case of smallpox in Mexico occurred in 1951, just after the Pan American Health Organization had launched its programme to eradicate smallpox from the Western Hemisphere (Rodrigues, 1975).

SMALLPOX IN SOUTH AMERICA, 1900–1958

Variola major was endemic in all the larger countries of South America during the first decade of the 20th century (Fig. 8.6), with the highest incidence in Brazil and Chile (Table 8.9). Reporting was very poor; indeed, many countries concealed the existence of smallpox for fear of the imposition of quarantine restrictions by their neighbours (Low, 1918).

In 1910 variola minor was reported from South America for the first time, in Brazil, where eventually it displaced variola major, which remained common in Argentina and Chile in the 1920s. Epidemics of variola major were reported in Colombia in 1943 and 1947, in Bolivia in the 1940s, and in Ecuador up to 1962. The last large outbreak of variola major in South America caused nearly 10 000 deaths in Peru in 1941–1943. Within a few years of the decision by the Pan American Sanitary Organization in 1950 to eradicate smallpox from the Western Hemisphere, Peru, Uruguay and Venezuela had eliminated the disease. Bolivia, Colombia, Ecuador and Paraguay followed in the early 1960s. By 1967, smallpox was still endemic only in Brazil, although there were importations from Brazil into Argentina, French Guiana and Uruguay after that date (Fig. 8.7).

Brazil

By far the largest and most populous country in South America, Brazil experienced severe epidemics of variola major early in the 20th century. Following a major epidemic in 1904–1905 (3800 deaths in Recife; 3600 deaths in Rio de Janeiro) the Brazilian government passed a bill requiring compulsory vaccination, but an antivaccination campaign led to open revolt with riots. Large epidemics with many deaths occurred in 1907–1910.

Fig. 8.6. Mexico, Central and South America: year in which smallpox ceased to be endemic in each country (national boundaries as of 1982). Dates in parentheses (for Honduras and Peru) indicate the initial elimination of endemic smallpox, after which endemicity was again established before final elimination in the year shown.

Table 8.9. South America: numbers of reported cases of smallpox in selected countries, 1920–1958[a,b]

	Brazil[c]	Argentina	Colombia[c]	Peru	Chile[c]	Venezuela	Bolivia	Ecuador	Uruguay	Paraguay
1920 population (millions)	27	9	6	5	4	2	2	1.5	1.9	0.7
1958 population (millions)	68	20	15	9	7	7	3	4	2	2
1920	*99*	..	..	..	15	..	..	..	..	..
1921	*49*	..	..	..	11 701	..	..	..	31	..
1922	*117*	..	..	..	8 494	..	..	..	0	..
1923	*40*	..	..	..	3 502	..	..	158	569	..
1924	13	..	..	..	410	..	..	9	176	..
1925	746	..	..	..	*26*	..	..	1	15	..
1926	4 146	..	..	..	*15*	..	..	1	4	..
1927	107	..	*444*	7	*14*	..	..	16	0	2
1928	2	..	*524*	..	*14*	..	..	196	0	0
1929	0	..	*254*	..	*11*	..	..	31	4	0
1930	2	..	*308*	..	*2*	28	..	374	0	0
1931	1	..	*206*	..	*5*	13	716	505	8	0
1932	95	..	..	1 164	0	2	10	203	11	0
1933	112	..	419	363	0	6	293	234	1	0
1934	0	..	742	502	0	2	618	237	8	0
1935	17	..	298	444	7	3	490	89	2	14
1936	23	545	640	248	0	70	220	58	53	6
1937	121	80	557	69	5	105	289	401	72	11
1938	93	53	453	97	0	256	235	18	29	..
1939	86	19	2 787	173	0	3 839	348	23	4	2
1940	123	0	1 992	371	0	955	342	3	2	..
1941	126	0	1 334	3 131	0	265	211	..	1	8
1942	79	120	1 443	2 499	0	259	205	10	0	..
1943	444	6	2 659	1 826	0	268	300	12	0	..
1944	1 234	41	1 445	296	38	610	1 159	28	0	..
1945	830	0	442	292	0	1 055	1 793	32	104	..
1946	1 234	71	396	700	0	2 114	1 033	144	167	124
1947	862	46	4 903	537	0	4 767	500	2 846	326	807
1948	1 288	140	7 356	7 105	6	5 685	831	3 616	0	113
1949	670	500	3 040	6 305	9	3 672	805	660	9	6
1950	749	4 788	4 818	3 753	3 564	3 062	644	251	3	304
1951	1 190	1 404	3 844	1 218	46	567	759	174	0	282
1952	1 668	982	3 235	1 360	15	453	590	665	16	797
1953	923	309	5 526	172	12	72	429	708	7	770
1954	1 035	256	7 203	115	1	113	624	2 516	1	207
1955	2 580	55	3 404	0	0	2	372	1 831	45	57
1956	4 718	86	2 572	0	0	4	499	669	42	132
1957	2 661	335	2 145	0	0	0	1 310	913	2	103
1958	2 190	27	2 009	0	0	0	183	863	0	21

[a] A horizontal line beneath a figure indicates that this represents the last probable occurrence of endemic smallpox.
[b] .. = no data recorded.
[c] Figures in italics denote the number of reported deaths from smallpox.

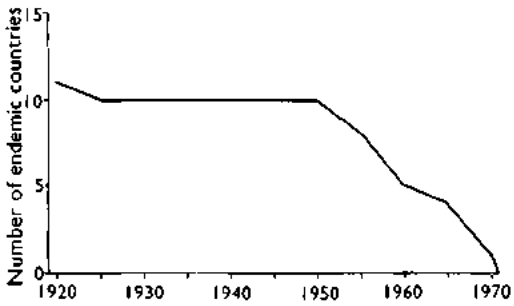


Fig. 8.7. Number of countries of the 13 in South America in which smallpox was endemic at various times between 1920 and 1971. National boundaries as of 1982.

Variola minor was introduced into Bahia from the USA in about 1910, whence it spread to the southern states of Brazil and eventually throughout the country, producing an estimated 250 000 cases in 1910–1911 (Aragão, 1911). During the outbreak in Paraná in 1910, some 6000 persons were infected but the case-fatality rate was only 2.3% (Carini, 1911). Mortality data over the next 20 years show that variola minor gradually replaced variola major as the commoner form of smallpox in Brazil, but as late as 1926 an epidemic of variola major in Rio de Janeiro caused 2200 deaths.

Although there were very few notifications over a period of several years in the late 1920s and early 1930s, variola minor had become established as an endemic disease and several thousand cases were notified every year from 1955 onwards. Further, Brazil became a major source of transmission of the disease to neighbouring countries, especially Argentina, a risk which continued until smallpox was finally eradicated from Brazil and thus from the whole Western Hemisphere in 1971.

Other Countries

In most of the other countries of South America variola major was common and severe during the first two or three decades of the 20th century and was then replaced by variola minor. The latter declined in incidence and was finally controlled in the 1950s and 1960s (Fig. 8.6), although importations from Brazil continued to occur. Ecuador was unusual in that variola major persisted at a relatively high level until the early 1960s.

SMALLPOX IN ASIA, 1900–1958

Asia is by far the most heavily populated continent, and China and India, vast countries with weak national public health services during the early part of this century, have long been regarded as the traditional homes of smallpox. The decline in the number of endemic countries in Asia since 1920 is shown in Fig. 8.8. Asia was the major focus of variola major throughout the first half of the 20th century, and until about 1950 smallpox was endemic in all of the more populous countries of the continent. In order to simplify discussion of this vast region, the data on eastern Asia, the Indian subcontinent and Afghanistan, and south-western Asia have been summarized separately.

Though the records of smallpox in many countries of Europe during the first half of this century are incomplete and seriously underestimate the incidence, they are very much better than those of any other countries except Australia, Canada, Japan, New Zealand and the USA. Data for China and the countries between China and India are very incomplete and reports by public health workers have been used to supplement the information provided by the official figures.

EASTERN ASIA

In contrast to the situation on the Indian subcontinent, endemic smallpox was eliminated from most of the countries of eastern Asia before the initiation of the Intensified Smallpox Eradication Programme in 1967 (Table 8.10; Fig. 8.9).

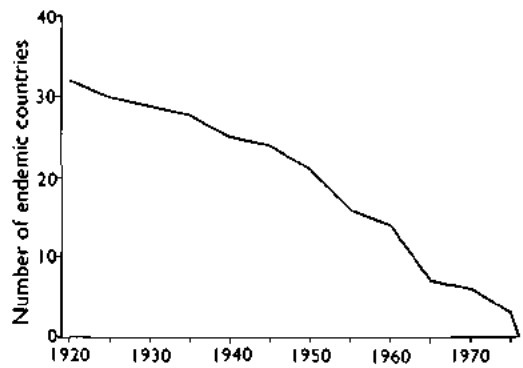


Fig. 8.8. Number of countries of the 38 in Asia in which smallpox was endemic at various times between 1920 and 1975. National boundaries as of 1982.

Table 8.10. Eastern Asia: numbers of reported cases of smallpox in selected countries, 1920–1966[a,b]

	China[c]	Japan	Netherlands East Indies (Indonesia)	Indochina[d]	Korea[e]	Burma[c]	Philippines	Thailand	Federated Malay States[f] (Malaysia)
1920 population (millions)	*ca.* 400	55	52	19	17	13	10	9	3
1950 population (millions)	554	84	80	34	30	18	21	20	7
1920	..	3 167	2 400	..	11 532	*2 853*	..	85	105
1921	*204*	889	1 445	..	8 316	*987*	..	404	232
1922	*230*	679	1 236	..	3 676	*1 439*	..	472	346
1923	*60*	1 922	4 922	..	3 722	*2 846*	..	1 451	73
1924	262	1 703	6 717	..	439	*2 501*	..	588	49
1925	554	430	4 681	4 753	699	*3 852*	20	287	66
1926	513	1 256	855	2 658	1 010	*2 339*	30	1 113	45
1927	110	352	766	745	626	*1 704*	1	418	391
1928	853	723	298	1 432	290	7 654	5	125	27
1929	927	114	614	4 954	523	8 205	367	405	57
1930	547	7	419	4 919	1 418	3 668	192	56	202
1931	617	21	176	2 058	1 376	2 022	4	33	193
1932	2 974	305	562	3 968	2 787	11 767	0	20	19
1933	2 969	375	57	2 969	4 928	7 701	0	42	5
1934	2 050	320	9	4 598	450	6 555	0	152	8
1935	502	113	43	3 655	1 273	4 974	0	34	177
1936	1 189	178	80	1 872	1 400	5 574	0	2	5
1937	1 444	90	1	3 053	204	6 365	0	51	24
1938	1 621	60	12	7 403	39	2 283	2	294	2
1939	3 551	287	2	4 772	625	702	..	151	1
1940	2 563	575	6	1 884	3 265	8 739	..	235	1
1941	12 720	654	..	1 272	4 720	5 593	..	107	1
1942	9 863	381	..	4 315	1 600	..	..	133	..
1943	6 466	546	..	5 060	1 284	..	..	44	..
1944	5 681	311	..	1 668	1 654	..	..	925	..
1945	5 464	1 614	..	..	..	6 778	..	36 394	..
1946	22 790	17 800	..	2 525	20 810	4 834	..	26 843	3 364
1947	23 164	386	..	4 572	402	3 939	0	1 314	4 529
1948	4 806	29	1 701	2 569	1 197	5 905	282	514	521
1949	862	124	13 413[g]	2 644	9 949	3 465	27	107	46
1950	50 575	5	99 016	396	2 349	10 222	0	348	0
1951	61 553	86	100 952	4 336	43 213	2 748	0	34	2
1952	10 388	2	9 802	4 024	1 377	2 411	0	43	2
1953	3 325	6	2 584	3 385	3 349	164	0	50	5
1954	856	2	1 875	4 007	790	216	0	20	0
1955	2 576	1	1 530	2 390	2	1 675	0	117	0
1956	587	0	2 817	1 531	9	4 226	0	4	0
1957	315	0	1 550	597	10	2 739	0	3	0
1958	671	0	3 202	53	6	1 897	0	28	0

Table 8.10 *(cont.)*

	China[c]	Japan	Netherlands East Indies (Indonesia)	Indochina[d]	Korea[e]	Burma[c]	Philippines	Thailand	Federated Malay States[f] (Malaysia)
1959	476	0	1 129	17	0	1 533	0	1 548	338
1960	23	0	5 196	0	3	392	0	32	15
1961	28	0	5 045	0	1	91	0	33	0
1962	2	0	3 435	1	0	32	0	2	0
1963	283	0	17 431	0	0	193	0	0	0
1964	35	0	17 213	0	0	112	0	0	0
1965	4	0	56 359	0	0	53	0	0	0
1966	0	0	35 283	0	0	6	0	0	5

[a] A horizontal line beneath a figure indicates that this represents the last probable occurrence of endemic smallpox.
[b] . . = data not recorded.
[c] Figures in italics denote the number of reported deaths from smallpox.
[d] Comprising present-day Democratic Kampuchea, Lao People's Democratic Republic, and Viet Nam.
[e] From 1951 onwards, the figures refer only to the Republic of Korea.
[f] Including Singapore.
[g] In Annex 1 of the *Final Report of the Global Commission for the Certification of Smallpox Eradication* (World Health Organization, 1980), the figure given for 1949 is 490 348. This seems an unlikely figure for the number of reported cases at that time (see Chapter 13). It derives from Henneberg (1961) and is not supported by data in the *Epidemiological and vital statistics report*, from which the figures in this table were derived.

Table 8.11. China: locations of smallpox vaccine production institutes and other particulars of vaccine production in 1950, when the national smallpox eradication campaign commenced, and in 1979. (The central assay and research laboratory was located in another institute in Beijing.)

1950			1979				
City	Province or municipality	Type[a]	City	Province or municipality	Control	Type[a]	Supply zone
Beijing	Beijing[b]	CL	Beijing	Beijing[b]	State	TC, some F-D	North China
Shanghai	Shanghai[b]	CL	Changchun	Jilin	State	CL and TC	North-east China
Dalian (Dairen)	Liaoning	CL	Lanzhou	Gansu	State	TC	North-west China
Kunming	Yunnan	CL	Chengdu	Sichuan	State	TC	South-west China
Lanzhou	Gansu	CL	Wuhan	Hubei	State	CL and TC, some F-D	South-Central and border areas
			Ji'an	Jianxi	Province	CL	East China
			Guangzhou (Canton)	Guandong	Province	CL	Guandong
			Zhengzhou	Henan	Province	CL	Henan

[a] CL = calf lymph; TC = tissue culture; F-D = freeze-dried.
[b] Municipality.

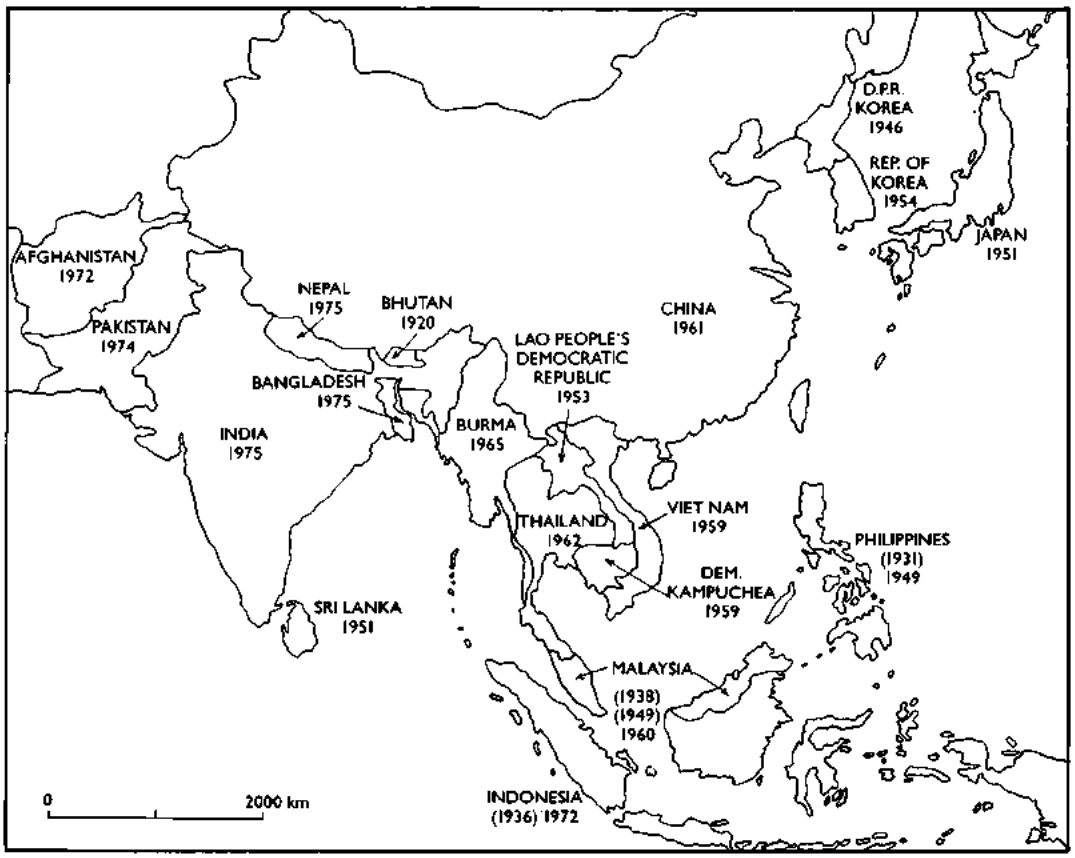


Fig. 8.9. East and South-East Asia: year in which smallpox ceased to be endemic in each country (national boundaries as of 1982). Dates in parentheses (for Indonesia, Malaysia and the Philippines) indicate the initial elimination of endemic smallpox, after which endemicity was again established before final elimination in the year shown.

For the first 3 decades of the 20th century smallpox was endemic throughout the mainland countries of eastern and south-eastern Asia, in Japan and in the larger island groups. Tibet, in which vaccination was not practised at all until 1940, suffered very severely, leading to the depopulation of some areas, and in China smallpox was regarded as something that every child had to get sooner or later. However, although there were still some severe epidemics, the incidence of smallpox declined in Japan, and notable early successes in eradication were recorded in the Philippines in 1931 and in the Netherlands East Indies (Indonesia) and the Federated Malay States (Malaysia) later that decade.

The disruption of services that accompanied and followed the Second World War led to a reappearance or resurgence of smallpox in several countries of eastern as well as of southern Asia. In Thailand, in which the annual number of reported cases had been less than 1000 for many years, there was a major epidemic in 1945–1946, with more than 62 000 reported cases. Smallpox was reintroduced into Malaysia in the early 1940s and was not eliminated until 1949, and into the Philippines in 1948, but was eliminated again in 1949. Over 20 000 cases were notified in Korea in 1946, and a major epidemic, with upwards of 43 000 cases, occurred in 1951, during the hostilities in that country. The incidence in Japan rose to 17 800 in 1946, and smallpox was reintroduced into Indonesia in 1947, reaching epidemic proportions in 1949.

The fact that smallpox had been eliminated in Europe and North America was a powerful stimulus for the declaration by the World Health Assembly in 1959 that global eradication was a goal that could be achieved. Although it was not fully appreciated, even more impressive achievements—and more

relevant to the eradication of smallpox from the impoverished countries of Africa and the Indian subcontinent—were then in progress in China, the Korean peninsula and the countries of Indochina. The elimination of the disease in China will be described in some detail, since it ranks with eradication from India as one of the most significant achievements in the struggle against smallpox. Aspects of importance in the certification of smallpox eradication in China are described in Chapter 27.

China

Smallpox was highly endemic throughout China for the first 4 decades of the 20th century, but no data were recorded except for the Treaty ports, from which most of the early figures in Table 8.10 were derived. Even here, they were gross underestimates. In Shanghai, as in the rest of China, smallpox was a seasonal disease, with a high incidence in winter and spring (from December to the end of May) and a low incidence during summer (Dold, 1915; Xu & Jiang, 1981). The disease was endemic, with epidemics in 1902, 1904, 1907, 1910 and 1913 (Dold, 1915) and between 1930 and 1951 there were epidemics in 1930–1934, 1936–1939, 1946–1948 and 1950–1951. Anecdotal data (Korns, 1921) reveal that smallpox was still wellnigh universal throughout China in the early 1920s; of 3020 adult males whom Korns questioned in an outpatient clinic, only 40 of 822 who had not been vaccinated had escaped the disease. Chinese with obvious pockmarks were very common in the streets of every city.

Variolation was practised on a small scale from about the 10th century (Needham, 1980) until the 1960s; outbreaks of smallpox in northeastern Yunnan Province in 1958 and in Nei Monggol Autonomous Region (Inner Mongolia) and Shanxi Province in 1963–1965 were attributed to variolation (see Chapter 27). From 1803 vaccination was occasionally available for those who could afford it. There were attempts to promote vaccination, notably after the establishment of the First Republic in 1913, but it was not practised at all extensively until the national smallpox eradication programme was instituted by the People's Republic of China in 1950.

Immediately after Liberation in 1949 a national campaign was launched to eradicate smallpox from China. The data published in European languages are very limited (SME/79.10; SME/79.11, Fenner & Breman; WHO/SE/79.142 Rev.1; WHO/SE/79.151; Xu & Jiang, 1981), but give some impression of the nature and progress of this campaign. A particularly interesting feature was that eradication was achieved in all the cities and larger towns within 5 years, and throughout the country in 11 years, by the vigorous prosecution of mass vaccination, using liquid vaccine.

China has extensive areas of agricultural land supporting over 100 persons per square kilometre (Fig. 8.10) and many large cities. The population in 1950 was about 600 million. In contrast to the eastern part of the country, population densities throughout the whole of western China were very low and these parts were thus areas in which the endemic transmission of smallpox was unlikely to persist.

In October 1950, the State Council of the Central Government issued a "Notice on the Campaigns for Smallpox Vaccination of Autumn 1950" which expressed the formal decision to carry out a mass vaccination campaign for the whole population of mainland China. At the same time, the Ministry of Health announced "Temporary Regulations for Smallpox Vaccination", ruling that all children should be vaccinated 6 months after birth and revaccinated at the ages of 6, 12 and 18 years. The scheme of operation was developed by the Ministry of Health and comprised a massive propaganda campaign to enlist the support of the population (a "Mass Patriotic Health Movement"), the organization of the production and distribution of vaccine from 5 vaccine institutes located in various parts of the country, the mobilization and training of vaccinators and an intensive effort to achieve universal vaccination, mostly during the year 1951. The scheme also involved measures to control the possible spread of smallpox by travellers within China, by rail, sea and river (see below).

The 5 vaccine institutes, which produced liquid calf vaccine of the Temple of Heaven strain (see Chapter 11), were located in Beijing, Shanghai, Dalian (Dairen), Kunming and Lanzhou. There were initially some difficulties in producing enough vaccine for the campaign. Later some of these institutes ceased production, and new production centres were established (Table 8.11). Meetings were held to improve various aspects of vaccine production and eventually (after eradication had been achieved) freeze-dried

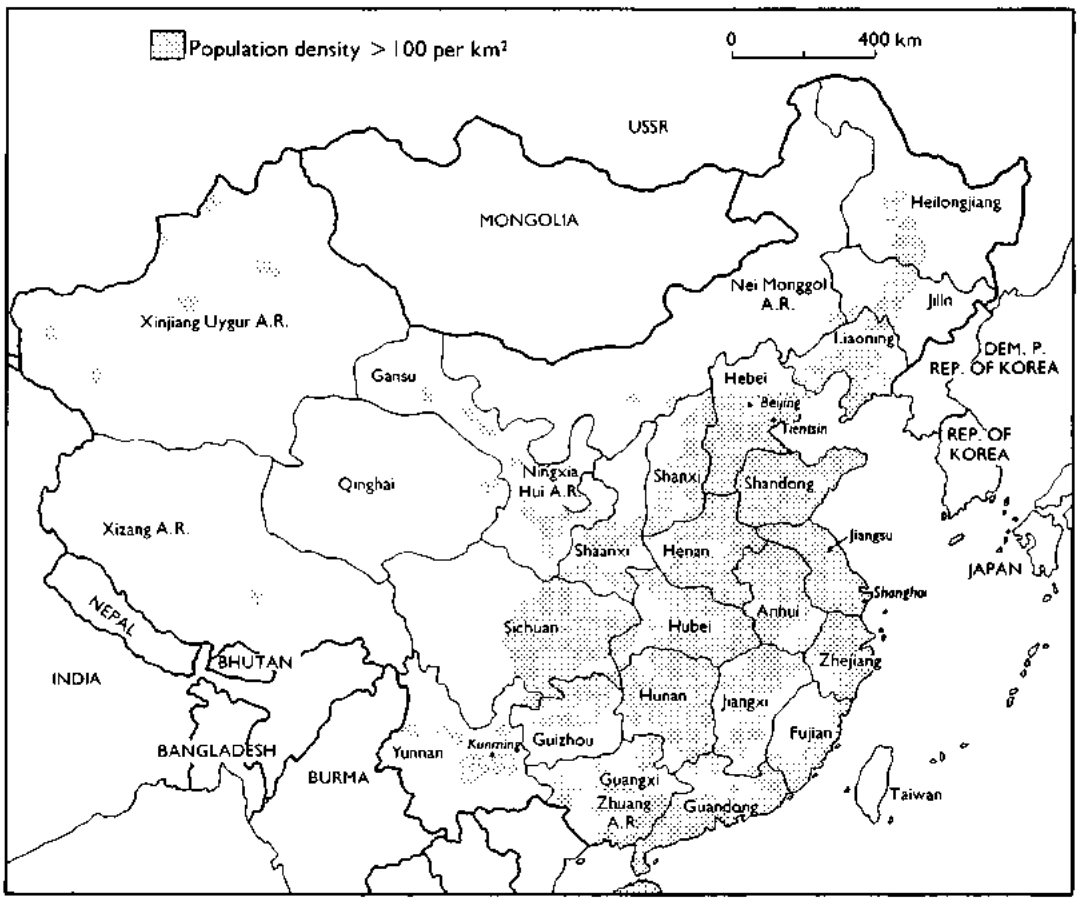


Fig. 8.10. China, showing the neighbouring countries and the provinces, autonomous regions and municipalities (internal boundaries as of 1985). The stippled area indicates regions where the population density is over 100 persons per square kilometre.

vaccine was produced for use in border and tropical areas. Vaccination was carried out by multiple pressure or the scratch technique, in 2 sites. The annual numbers of vaccinations performed throughout China during and immediately after the eradication campaign are suggested by the numbers of doses of vaccine issued (Table 8.12).

In 1955, following the endorsement by the State Council of the Central People's Government, the Ministry of Health produced a booklet, *Methods of Control of Communicable Diseases*, which provided for the compulsory notification of 24 diseases including smallpox. Between 1955 and 1958 a second country-wide mass vaccination campaign was undertaken, with technical aid provided by the USSR under the Socialist Pact of Friendship of 15 February 1950. This highly organized campaign operated airlifts in remote regions and was assisted by large numbers of personnel from Czechoslovakia and Hungary. However, relations with the USSR gradually deteriorated with disagreements on borders and ideology, and by 1961 the assistance agreements had been cancelled.

The number of administrative divisions reporting cases dropped from 21 in 1953 to only 1, Yunnan, in 1959 (Table 8.13), although cases occurred in 2 localities in

Table 8.12. China: numbers of doses of smallpox vaccine issued, 1950–1963[a]

Year	Number of doses (millions)	Year	Number of doses (millions)
1950	129	1957	100
1951	160	1958	99
1952	264	1959	118
1953	165	1960	84
1954	99	1961	170
1955	96	1962	110
1956	107	1963	100

[a] From WHO/SE/79.142 Rev. 1.

Table 8.13. China: numbers of smallpox cases reported, 1950–1965, by administrative division[a,b,c]

	1950	1951	1952	1953	1954	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965
Provinces																
Anhui	1 266	705	91	19	2	0	0	0	0	0	0	0	0	0	0	0
Fujian	2 292	455	22	1	0	0	0	0	0	0	0	0	0	0	0	0
Gansu	473	969	135	14	7	5	2	1	0	0	0	0	0	0	0	0
Guangdong	1 395	8 066	1 045	16	4	0	0	0	0	0	0	0	0	0	0	0
Guizhou	2 428	5 713	1 788	52	2	0	0	0	0	0	0	0	0	0	0	0
Hebei	6 410	262	13	1	0	0	0	0	0	0	0	0	0	0	0	0
Heilongjiang	1 043	75	115	8	8	0	0	0	0	0	0	0	0	0	0	0
Henan	7 461	780	241	29	406	0	6	0	1	0	0	0	0	0	0	0
Hubei	4 783	2 734	133	22	0	0	0	0	0	0	0	0	0	0	0	0
Hunan	2 848	3 155	110	3	0	1	0	0	0	0	0	0	0	0	0	0
Jiangsu	729	3 613	553	0	0	0	0	0	0	0	0	0	0	0	0	0
Jiangxi	1 597	624	58	0	0	0	0	0	0	0	0	0	0	0	0	0
Jilin	206	186	18	14	6	2	0	0	0	0	0	0	0	0	0	0
Liaoning	2 081	113	48	7	3	0	0	0	0	0	0	0	0	0	0	0
Qinghai	76	20	49	67	0	0	0	0	0	0	0	0	0	0	0	0
Shaanxi	1 336	431	211	14	9	4	0	0	0	0	0	0	0	0	0	0
Shandong	0	923	454	67	0	0	0	0	0	0	0	0	0	0	0	0
Shanxi	241	162	76	0	0	0	0	0	0	0	0	0	0	28	0	4
Sichuan	6 100	11 584	1 196	226	181	18	138	108	0	0	0	0	0	0	0	0
Taiwan	78	7	39	14	9	0	0	0	0	0	0	0	0	0	0	0
Yunnan	1 698	6 255	2 667	709	100	32	3	92	661	476	7	28	0	0	0	0
Zhejiang	417	664	26	0	0	0	0	0	0	0	0	0	0	0	0	0
Autonomous regions																
Guangxi Zhuang	3 569	10 662	1 085	13	0	0	0	0	0	0	0	0	0	0	0	0
Nei Monggol	1 103	340	151	19	7	7	1	0	0	0	0	0	1	255	30	0
Ningxia Hui	..	..	..	..	..	0	0	0	0	0	0	0	0	0	0	0
Xinjiang Uygur	..	321	64	2 010	112	2 484	433	114	9	0	0	0	0	0	0	0
Xizang	..	..	..	..	..	23	3	0	0	0	16	0	1[d]	0	5[d]	0
Municipalities																
Beijing	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Shanghai	927	2 734	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tianjin	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total (including Taiwan)	50 575	61 553	10 388	3 325	856	2 576	587	315	671	476	23	28	2	283	35	4

[a] No cases reported after 1965.
[b] Data from Jiang (1985; and personal communication, 1987).
[c] .. = data not recorded.
[d] Importations.

Xizang Autonomous Region (Tibet) in 1960 and there were importations from Nepal in 1962 and 1964. Smallpox remained endemic in the south-west part of Yunnan, where there was a common border with Burma, until 1961 (see Chapter 27).

Information that only became available very recently (Jiang Yutu, 1985; and personal communications, 1984, 1987) reveals that smallpox continued to occur in China until 1965. In 1962, 6 years after the last reported case in the Nei Monggol Autonomous Region, 1 case was reported there, and in 1963 an outbreak of 283 cases occurred in Nei Monggol and nearby counties of Shanxi Province, with a further 30 cases in 1964. Another small outbreak (4 cases) occurred in Shanxi in 1965. Both the 1962–1964 and the 1965 outbreaks were attributed to the activities of variolators (see Chapter 27).

In 1959, because several outbreaks of smallpox had occurred following the importation of cases from neighbouring countries into China, it was decided to implement another general mass vaccination campaign. This began in 1960 and aimed to reinforce the achievement of the virtual elimination of smallpox and to raise the level of herd immunity and thus prevent the transmission of smallpox in the event of its importation into the country. Border areas were given first priority.

The method of implementation of the mass vaccination campaigns, in 1949–1952, 1955–1958 and in 1960, was unique. A directing committee of leaders was organized by the joint efforts of the health authorities and epidemic prevention departments in every province, municipality, and autonomous region. The committee was responsible for the organization of local health personnel and the training of medical and paramedical workers to form vaccination teams and perform the vaccinations. The teams went to each village or courtyard to vaccinate all persons, using the lists of names of members of the brigade or courtyard. Children in kindergartens and schools were vaccinated at these locations. During the first visit it was possible to vaccinate nearly 90% of the people. Others were vaccinated in the health centres or polyclinics. Members of governmental bodies, institutions, factories, etc., were vaccinated in health service facilities located at their place of work. After the communes were established in 1958, monthly payments by the State were linked to evidence of vaccination of the family head and family members.

No general account of the country-wide smallpox eradication campaign in China has been published, but operations in the country's largest city and centre of communications, Shanghai, have been described (SME/79.11, Fenner & Breman; Xu & Jiang, 1981) and provide an idea of how the programme operated there and elsewhere. Details of special surveys made in Yunnan Province and in Xizang (Tibet) for certification purposes are described in Chapter 27.

Shanghai municipality

Smallpox had always been endemic in Shanghai, with frequent epidemics, and before the eradication campaign was launched the overall vaccination rates were low (Table 8.14). A severe epidemic began in December 1950, 2 months after the promulgation of the eradication campaign. Although deaths and especially cases were underreported, 3167 cases and 1482 deaths were recorded for the 5 months December 1950 to April 1951.

The aim of the campaign in Shanghai was to vaccinate at least 95% of the population in the shortest possible time. In order to accomplish this, 6944 medical and paramedical personnel were organized into 1319 permanent stations and 1836 mobile vaccination teams. The personnel, comprising 3173 doctors of Chinese traditional medicine, 2067 doctors of western medicine, 455 nurses and midwives, 1126 medical students, and 123 others, were given a short training course in order to standardize the vaccination technique. The mass vaccination campaign began in March 1951. As the number of vaccinations rose (Table 8.15) and the weather became

Table 8.14. Shanghai: smallpox vaccination, 1946–1951[a]

Year	Population	Number of persons vaccinated	Ratio: $\frac{\text{Vaccinations}}{\text{Population}} \times 100$
1946	3 536 209	536 573	15.2
1947	3 925 621	2 251 096	57.3
1948	5 204 321	2 464 609	47.4
1949	5 406 644	1 447 609	26.8
1950	5 063 818	2 232 340	44.1
1951	5 333 036	6 925 363[b]	129.9[b]

[a] From Xu & Jiang (1981).

[b] Includes visitors, travellers, and persons vaccinated more than once.

Table 8.15. Shanghai: cumulative proportion of vaccinations relative to population and the incidence of smallpox in 1951[a]

Month	Cumulative vaccination rate (%)[b]	Number of reported smallpox cases
January	11.5	958
February	19.1	646
March	88.1	722
April	108.0	325
May	110.3	55
June	110.4	18
July	110.5	10
August	110.6	0

[a] From Xu & Jiang (1981).
[b] Includes visitors, travellers and persons vaccinated more than once.

hotter, the incidence of smallpox fell. The last case in Shanghai was reported on 26 July 1951.

During the early 1950s there was little international travel through Shanghai, but it was a major national communications centre, by sea, river, road and rail. The Quarantine Service was organized to cope with travellers by boat and train to other parts of China, as well as with boat-dwellers on the Huangpu and adjacent rivers. In the case of travellers by boat, ships' crews were mobilized to assist the campaign by propaganda and by forming "health groups" among them. Crew members were urged to report all cases of smallpox, among passengers or crew. An elaborate system was developed for supervising the issue of internal vaccination certificates for both boat and train travellers within China, with facilities for immediate vaccination if necessary.

Among the boat-dwellers on the Huangpu, in all 76 221 vaccinations were performed in 1951. Nine cases of smallpox were discovered on 5 boats; all case contacts were vaccinated and no other cases occurred. Among travellers and boat crews, 785 321 persons were vaccinated. On the 3576 boats that left Shanghai in 1951, 7 cases of smallpox were detected among passengers before boarding and 28 after boarding. In the first 4 months of 1951, 72 cases of smallpox were detected among intending train travellers. The effectiveness of this system of surveillance of travellers within China was demonstrated by the fact that although there was a major epidemic in Shanghai at the time, there was little apparent spread to other parts of China.

Japan

Smallpox was endemic in Japan during the latter part of the 19th century, and during the early 20th century the country was constantly exposed to the risk of imported cases, owing to its large maritime trade and its proximity to China, Korea, Manchuria and Siberia, in all of which smallpox was a common disease at that time. Table 8.16 sets out the numbers of reported cases of and deaths from smallpox in Japan between 1892 and 1915.

Institutes for the production of vaccine in calves had been operating in Japan since 1874, and in 1891 arm-to-arm vaccination was prohibited. In 1896 celebrations were held in Ueno Park in Tokyo to mark the centenary of Jenner's discovery, and at about this time the famous bacteriologist Kitasato made important contributions to the preparation of bacteriologically sterile vaccine and helped to promote its use (Soekawa, 1984). In consequence of the gradual extension of vaccination the incidence of the disease fell. There was a severe epidemic in 1908, but thereafter smallpox continued to decline. In 1918 vaccination was made mandatory for all 1-year-old children and revaccination was carried out at school entry. The incidence fell further, and between 1927 and 1944 only 5412 cases were

Table 8.16. Japan: numbers of reported cases of and deaths from smallpox, 1892–1915[a,b]

Year	Number of cases	Number of deaths	Case-fatality rate (%)
1892	33 779	8 409	24.9
1893	41 898	11 852	28.2
1894	12 418	3 342	26.9
1895	1 287	268	20.8
1896	10 704	3 388	31.6
1897	41 946	12 276	29.4
1898	1 752	362	20.6
1899	1 215	245	20.1
1900	111	4	3.6
1901	92	4	4.3
1902	46	7	15.2
1903	72	6	8.3
1904	1 118	237	21.2
1905	278	62	22.3
1906	496	109	21.9
1907	1 034	437	42.2
1908	18 067	5 837	32.3
1909	106	26	24.5
1910	80	15	16.2
1911	202	34	16.8
1912	14	1	7.4
1913	108	53	49.1
1914	485	110	22.6
1915	17	3	17.6

[a] Based on Low (1918).
[b] Population of Japan in 1913: 53 million.

reported (see Table 8.10). With the ending of the Second World War and the repatriation of Japanese soldiers, smallpox broke out again, with 1614 reported cases in 1945 and 17 800 in 1946. Shortly after this, control measures were further strengthened and smallpox ceased to be endemic in Japan in 1951.

Korea

Korea was for several centuries an independent state within the Chinese cultural orbit, and its history of smallpox parallels that of China. In 1910 it was formally annexed by Japan, having for the 5 preceding years been a virtual protectorate of that country, but after the defeat of Japan in the Second World War, Korea was divided at the 38th parallel of latitude and separate governments have operated in the north and the south since 1953. During the period in which it was under Japanese control (1905–1945) the enforcement of country-wide vaccination reduced the prevalence of smallpox, but variola major remained endemic, with case-fatality rates in different outbreaks varying between 20% and 27%. There was a more severe epidemic than usual in 1940–1941, and the disruption after the Second World War led to a major exacerbation in southern Korea, with over 20 000 reported cases in 1946 and over 43 000 cases in 1951, during the hostilities (see Table 8.10). The situation was rapidly brought under control after the conclusion of the conflict, and endemic smallpox was eliminated in 1954.

Indonesia

Severe outbreaks of smallpox occurred in various parts of the Netherlands East Indies in the early part of the century, an outbreak in Borneo claiming 3000 lives in 1905 and another, in Java, in 1913, causing more than 18 000 cases, with 5000 deaths. A severe outbreak occurred in Java in 1918–1919 and during 1922 and 1924 it spread to the outer islands, the south-eastern part of Borneo and the east coast of Sumatra.

In the early 1920s several thousand cases were reported annually, mostly in Java, but the incidence declined steadily after 1926 (see Table 8.10). Polak (1968) attributes the fall to more complete and effective vaccination coverage of the population, which was achieved by a combination of administrative and technical factors. Administratively, a system of concurrent primary vaccination and revaccination, which had led to repeated revaccination of readily accessible subjects and inadequate primary vaccination coverage of infants, was replaced by a dual system with an allocated time for each. Primary vaccination of children aged 3–6 months was carried out by locally based vaccinators during the first 8 weeks of each quarter, and revaccination of the older population was performed during the last 5 weeks. Arrangements for supervision were also greatly improved. The main technical advance was the production by Otten (1927) of a stable air-dried vaccine for use in remote areas (see Chapter 7, Plate 7.3A). The control of smallpox did not depend just on mass vaccination, however, because it was the practice of the Dutch at that time vigorously to contain such outbreaks of smallpox as were found.

After 1933, about 10% of the population were vaccinated or revaccinated each year and by 1937 endemic smallpox had disappeared. Seven of the 21 cases reported between 1937 and 1940 (see Table 8.10) were documented as importations; the others were suspected to be importations or mistaken diagnoses (Polak, 1968). The disruption of the Second World War, during which the Netherlands East Indies and neighbouring areas of south-eastern Asia had been captured by the Japanese and then liberated in 1945, led to major epidemics of smallpox in neighbouring countries, especially Thailand and Malaysia. Smallpox was reintroduced into Sumatra from Thailand in 1947. This outbreak was controlled, but another importation from Malaysia led to a major epidemic in Java in 1949, with over 13 000 cases. This time the disease became firmly entrenched in the larger islands, but did not spread to the numerous but more sparsely populated islands to the east (see Chapter 13, Fig. 13.3). There was a sustained high incidence in 1950 and 1951, and although the number of reported cases fell after 1951, variola major remained endemic for some years after the Intensified Smallpox Eradication Programme was established in 1967. Eradication was finally achieved, for the second time, in 1972 (see Chapter 13).

Philippines

There were as many as 40 000 smallpox deaths annually in the Philippines at the turn of the century, and smallpox was implicated

in about one-third of the cases of blindness (Low, 1918). Intensive vaccination efforts were launched by the United States authorities and resulted in a dramatic reduction in the incidence of smallpox to some 700 cases in 1914. Because of its contacts with the USA, which had succeeded Spain as the occupying power between 1898 and 1918, the Philippines experienced what was probably variola minor (described locally as "varioloid") during the second decade of the 20th century (McVail, 1923), but it was always rare, according to reported figures, compared with variola major.

Control efforts were relaxed after the transfer of responsibility for health matters from the United States to the Philippine authorities in 1916, and a very severe epidemic occurred in 1918–1919, with over 64 000 deaths (McVail, 1923). Various inefficiencies and deceitful practices were exposed by inquiries into this disaster. Subsequently, vaccination efforts were greatly strengthened, with the result that the last cases of endemic smallpox occurred in the Philippines in 1931. Apart from a few outbreaks associated with importations—notably 282 reported cases in 1948 which persisted into 1949—the Philippines has remained free of smallpox ever since (see Table 8.10).

Malaysia

The smallpox situation in the Federated Malay States (Malaysia) before the Second World War was rather similar to that in Indonesia, the endemic disease being eliminated in the late 1930s (see Table 8.10). No figures are available for the war years (1942–1945) but by 1946 smallpox was well established again, with 3364 reported cases that year and over 4500 (1008 deaths) in 1947. The disease was rapidly curbed by control measures, and no endemic cases were reported after 1949, except for an outbreak of 338 cases in 1959 which extended into 1960, following an importation.

Burma

Burma was administered as part of British India until 1937, and gained its independence in 1948. As in India, smallpox was a traditionally important endemic disease, usually causing between 1000 and 8000 reported deaths per year, during the period 1905–1927 (Low, 1918; see Table 8.10) in a population that rose over this period from 8.5 to more than 13 million. The incidence continued to be high, especially in the provinces, but the seaports remained reasonably free of the disease, although there was a major epidemic in Rangoon in 1950 (Murray, 1951). By 1958 the annual incidence of reported cases was still over 1000. Control measures were gradually improved and the incidence fell to some hundreds of reported cases annually by 1960; the endemic disease was eliminated in 1965. The Chinese experience of importations across the border into Yunnan Province in 1960 (see Chapter 27) suggests that there was a good deal of unreported smallpox in the remote border regions of Burma.

Thailand

Thailand was one of the few Asian countries never to be colonized by a European power. In the early years of the century even the registration of deaths was limited to Bangkok, in which there was a very severe epidemic of smallpox in 1911–1912, with 2368 deaths in a population of about 600 000. In 1914, following this outbreak, vaccination was made compulsory, first in Bangkok and ultimately in the country as a whole. Prior to the outbreak of the Second World War smallpox appeared to be coming under control (see Table 8.10), but a rising incidence in 1944 was followed by severe epidemics in 1945 and 1946, with over 62 000 reported cases and 15 000 reported deaths. An intensive vaccination campaign brought the disease under control by the early 1950s, but there was a further outbreak, with over 1500 reported cases, in 1959, before the disease was eliminated in 1962.

Indochina

The present-day states of Democratic Kampuchea, Lao People's Democratic Republic and Viet Nam, which before 1954 constituted French Indochina, had long suffered from endemic variola major. Reporting was very incomplete, but there was an increased prevalence during the latter years of the First World War, said to have been due to the discontinuance of official vaccination tours by government medical officers. Smallpox continued to be endemic between the wars, increasing somewhat (but not as much

as in Thailand) just after the Second World War. Major efforts at control instituted by the newly independent countries achieved elimination in the late 1950s (Lao People's Democratic Republic, 1953; Democratic Kampuchea, 1959; and Viet Nam, 1959), which was fortunate, otherwise there might have been further outbreaks during the Viet Nam conflict of 1965–1975. However, no cases were reported then by either of the warring sides.

THE INDIAN SUBCONTINENT AND AFGHANISTAN

During the early years of the 20th century smallpox was endemic in all countries of southern Asia, and India had already emerged as the major focus of smallpox in the world, a position it retained until the disease was eradicated there in 1975. Smallpox remained endemic in all the countries of the Indian subcontinent except Sri Lanka (in which eradication was achieved in 1951) throughout the period under review (Table 8.17).

India

As vaccination coverage improved in British India the rate of reported deaths from smallpox gradually fell from over 2000 per million population in 1870 to less than 300 per million in 1930 (see Chapter 5, Fig. 5.2). A pattern of epidemics every 5–7 years was maintained, and even in non-epidemic years the disease caused many deaths and sometimes great disruption. For example, in 1930 smallpox afflicted all the port cities of India and in consequence other countries imposed severe restrictions on Indian shipping.

Although a Vaccination Act required that all children should be vaccinated within 6 months of birth, this was not enforced; indeed, it was not considered practicable to enforce compulsory vaccination in India. Since most older persons were immune on account of vaccination or a previous attack, smallpox was primarily a disease of children, with a very high mortality among those aged less than 1 year. By 1941 primary vaccination was legally compulsory in some 80% of towns and 60% of the villages in British India, but revaccination was compulsory only in Madras. However, by 1944 some 60 million vaccinations were being given annually in a population of about 332 million, using liquid vaccine produced in 14 laboratories situated in the different states.

In 1947 India obtained independence and the partition of British India into Pakistan (East and West) and India occurred, with the consequent readjustment of populations and reporting arrangements (Table 8.17). Large-scale vaccination continued, but many of the vaccinations were probably ineffective owing to the lack of potency and heat stability of the vaccine. However, because vaccination was readily available and variolation was legally forbidden, the latter practice ceased and was never a problem in India during the Intensified Smallpox Eradication Programme. There was little change in the situation until after 1962, when a national smallpox eradication programme was launched (see Chapter 15). Smallpox was not finally eliminated from India until May 1975.

Pakistan and Bangladesh

The situation was little different in India's neighbours, Pakistan and Bangladesh (East Pakistan until December 1971). Prior to partition in 1947 they had been part of British India, and a gradual increase in vaccination coverage had lowered the incidence of smallpox. In West Pakistan (Pakistan after December 1971) variolation was widely accepted as a control measure practised by Muslim religious leaders, and it continued to be used long after vaccination was introduced as a public health measure in 1875. After 1947 the Vaccine Institute in Lahore continued to prepare glycerolated liquid vaccine, but in spite of some 15 million reported vaccinations a year in West Pakistan (population in 1950, 40 million) endemic smallpox continued, especially in the cities and mainly in unvaccinated children. A variety of factors contributed to the failure of vaccination: substandard vaccine, inadequate motivation of the public, defective legislation, and lack of supervision of vaccinators. Eventually, after intensification of the national eradication programmes and help from the World Health Organization, the last case of smallpox was reported in October 1974.

There were large outbreaks in East Pakistan (Bangladesh) after partition, with 70 000 reported cases in 1950–1952 and over 100 000 cases in 1957–1958. In 1953 vaccine began to be produced by the Institute of Public Health in Dhaka. After 1958 only freeze-dried vaccine was produced, but until 1966 its quality was inferior. Smallpox was finally eliminated in October 1975.

Table 8.17. Indian subcontinent and Afghanistan: numbers of reported cases of smallpox in selected countries, 1920–1966[a]

	India[b,c]	Bangladesh (East Pakistan, 1947–1971)	Pakistan (West Pakistan, 1947–1971)	Afghanistan	Ceylon (Sri Lanka)
1920 population (millions)	250	–	–	6	5
1950 population (millions)	350	42	40	8	8
1960 population (millions)	431	52	50	10	10
1920	*98 476*			..	126
1921	*39 459*			..	18
1922	*39 397*			..	337
1923	*41 238*			..	175
1924	*52 879*			..	40
1925	175 490			..	28
1926	220 221			..	65
1927	222 615			..	27
1928	165 458			..	18
1929	148 827			..	8
1930	232 331			..	41
1931	89 249			..	9
1932	115 967			..	106
1933	252 748			..	337
1934	263 276			..	72
1935	282 346			..	115
1936	218 323			..	3
1937	105 209			..	2
1938	89 341			..	0
1939	133 616			..	1
1940	188 192			..	0
1941	143 515			..	167
1942	76 882			..	1
1943	136 826			..	135
1944	328 466			..	124
1945	289 074			..	711
1946	146 431			..	409
1947	69 039	..	4 282	..	1
1948	73 422	..	12 524	..	8
1949	74 930	..	4 807	393	2
1950	157 487	21 273	1 013	612	4
1951	253 332	38 871	3 866	1 299	*344*[d]
1952	74 836	10 490	8 519	2 179	25
1953	37 311	1 102	9 033	1 813	2
1954	46 619	445	4 320	1 767	1
1955	41 837	1 926	3 330	1 411	0
1956	45 109	4 962	423	1 002	0
1957	78 666	24 920	1 631	226	19
1958	168 216	79 060	3 485	306	29
1959	47 693	15 048	3 373	442	0
1960	31 091	1 905	815	109	0
1961	45 380	660	2 408	178	44
1962	55 595	610	3 484	288	66
1963	83 423	3 735	1 929	577	1
1964	40 265	69	935	178	0
1965	33 402	316	1 285	72	1
1966	32 616	3 207	2 936	66	0

[a] .. = data not recorded.
[b] Excluding Burma; see Table 8.10.
[c] Figures in italics denote the number of reported deaths from smallpox.
[d] The last probable occurrence of endemic smallpox.

Afghanistan

Afghanistan was internationally recognized as an independent state in 1921. In this rugged and sparsely populated country, smallpox remained endemic throughout the first half of the 20th century and variolation was extensively practised (see Chapter 14). In the 1930s, Berke (1956) set up the first modern-type vaccination service, and it was reported that about 3 million persons were vaccinated in the period 1936–1939. Vaccination was made compulsory in Afghanistan in 1959.

No information is available on the smallpox incidence prior to 1949. Thereafter, the number of reported cases varied between a few hundred and about 2000 annually, mostly in the towns. The incidence of smallpox in the large population of nomads and semi-nomads was unknown. Endemic transmission ceased in 1972.

Sri Lanka

Smallpox was much more readily controlled on the island of Ceylon (Sri Lanka) than on the adjoining mainland of India. Vigorous vaccination campaigns in the 1920s reduced smallpox to occasional outbreaks following importations from India; only 103 cases were reported between 1927 and 1931 (Table 8.17). Following another importation from India in November 1932 there was a larger outbreak, which extended into 1933, but this was followed by 5 years of virtual absence of the disease (1936–1940). As occurred elsewhere in Asia, there was a resurgence during the Second World War but control was re-established in 1947 and the elimination of endemic smallpox was claimed in 1951. Thereafter, importations from India caused small, readily controlled outbreaks in most years.

SOUTH-WESTERN ASIA

Prior to the First World War this region consisted of the Ottoman Empire and Persia. Smallpox was endemic and largely unreported in both areas. The holy cities of Mecca and Medina provided major foci for importations and subsequent exportations of smallpox to all parts of the Muslim world. With regard to Persia the statement was made at a meeting of the Teheran International Sanitary Council in 1907 that between 50 000 and 100 000 persons died annually from smallpox (Low, 1918).

Between the First and Second World Wars the reported incidence of smallpox fluctuated in Persia and the new states that arose out of the Ottoman Empire (Fig. 8.11), but had fallen to a low level in most countries of the area by the late 1930s (Table 8.18). An epidemic focus developed in Iraq in 1940-1941, with over 3000 reported cases, and in 1942 spread westwards into Syria, Lebanon, Turkey, Palestine and Jordan and eastwards into Iran. In 1943 there was a major outbreak in Turkey which extended into Greece (see Table 8.2). Intensive vaccination campaigns were instituted in Turkey and the endemic disease was eliminated by 1951, but substantial numbers of cases continued to be reported from Iran and Iraq until the late 1950s

The Incidence of Smallpox on Islands

Island countries with sparse populations were spared endemic smallpox because their populations were too small to sustain continuous transmission, and they were much less frequently subject to importations than were countries of a similar size and population located on the continental mainland. The outstanding examples are Australia and New Zealand, both of which were colonized by British settlers after the concept of quarantine was established, and were so distant from smallpox-endemic countries that persons incubating the disease on embarkation were sick on arrival and were discovered during quarantine inspections. Other examples mentioned in this chapter are Sri Lanka and Madagascar, in each of which importations were less frequent and more easily controlled than in countries with comparable populations on the adjacent continents, such as Nepal and Mozambique. Locally produced liquid vaccine was more likely to be potent when administered than in continental countries, because of the short distances and, therefore, speedier delivery from production centres to villages. Very remote islands were either spared the disease entirely or subject to widely spaced devastating epidemics such as occurred in Iceland before 1870. If the population of the island was dense enough, however, as in Java, endemic smallpox could be firmly established and proved difficult to climinate.

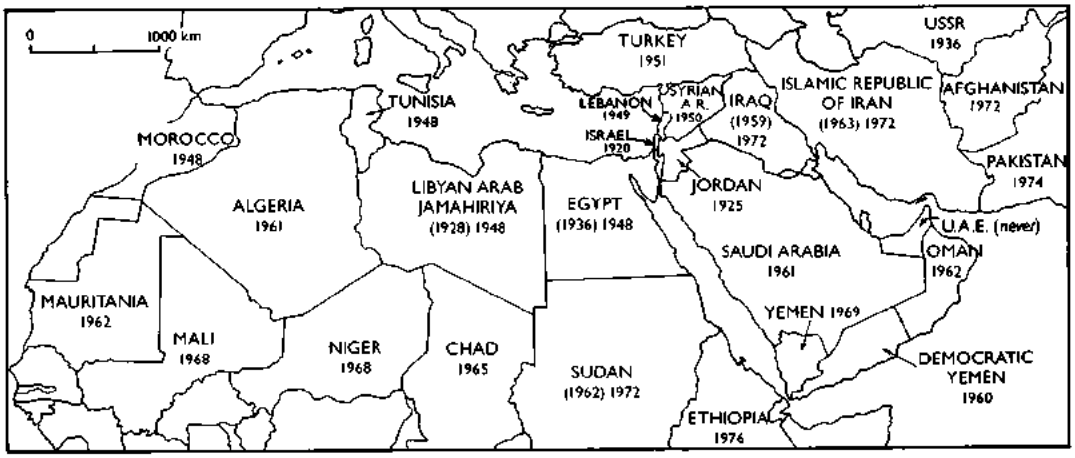


Fig. 8.11. North Africa and south-western Asia: year in which smallpox ceased to be endemic in each country (national boundaries as of 1982). Dates in parentheses (for Algeria, Egypt, Iraq, Islamic Republic of Iran, Libyan Arab Jamahiriya and Sudan) indicate the initial elimination of endemic smallpox, after which endemicity was again established before final elimination in the year shown.

and early 1960s. Endemic smallpox was re-established in Iran, Iraq and the Syrian Arab Republic in 1971–1972, but then brought under control (see Chapter 23).

SMALLPOX IN AFRICA, 1900–1958

Although smallpox arrived in some countries in central Africa as late as the 19th century (see Chapter 5), the disease was firmly entrenched throughout the continent during the first quarter of the 20th century. Variola major predominated in most places, but variola minor occurred concurrently in many countries in southern and eastern Africa. Vaccination was practised less than variolation, but both were uncommon. Tulloch (1980) reviewed the incidence of smallpox in different countries in Africa over the half-century between 1928 and 1977; the changes in incidence over the 3 decades 1938–1967 are illustrated in Fig. 8.12. The continued endemicity of smallpox in all countries of Africa

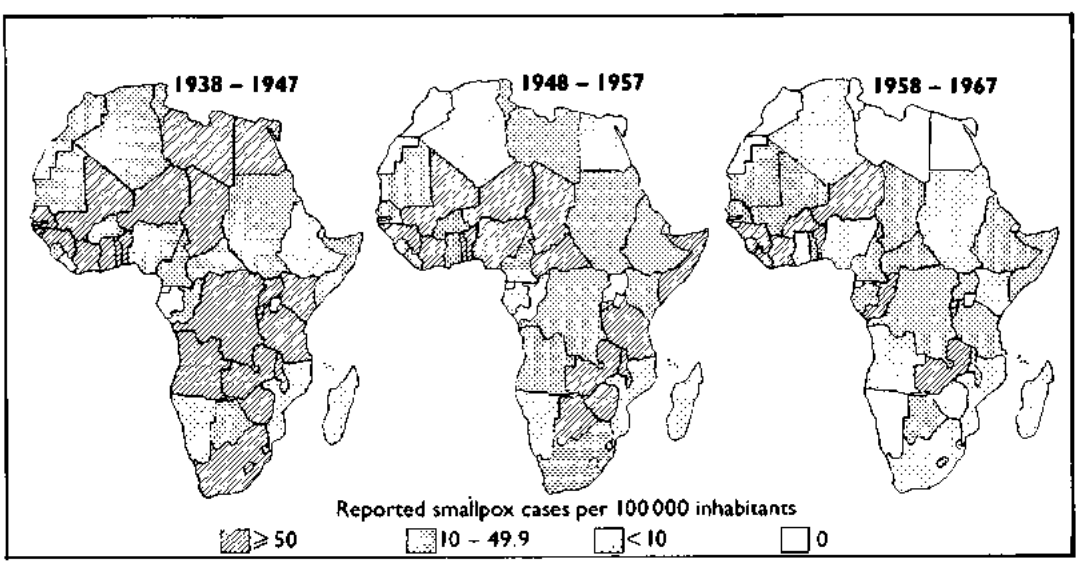


Fig. 8.12. Africa: maximum reported annual incidence rates of smallpox during each decade, 1938 – 1967. No data available for Equatorial Guinea, 1938 – 1947. (From Tulloch, 1980.)

Table 8.18. South-western Asia: numbers of reported cases of smallpox in selected countries, 1920–1963[a,b]

	Iran	Turkey	Saudi Arabia	Iraq	Syrian Arab Republic
Population (millions)	16 (1937)	14 (1927)	3 (1950)	4 (1934)	2 (1937)
1960 population (millions)	20	28	4	7	5
1920	..	6	..	..	..
1921	..	..	..	475	..
1922	..	253	..	1 862	..
1923	..	2 492	..	1 692	60
1924	..	1 615	..	459	40
1925	..	971	..	832	46
1926	..	480	..	1 062	1
1927	..	99	51	761	98
1928	..	47	425	1 956	488
1929	446	1 746	525	2 374	375
1930	191	830	291	762	158
1931	552	257	606	744	6
1932	1 745	193	212	2 318	109
1933	765	199	145	1 260	435
1934	203	93	306	387	1 011
1935	91	107	187	264	48
1936	84	69	43	198	1
1937	34	36	8	28	0
1938	25	641	1	39	0
1939	278	438	1	111	1
1940	316	958	255	1 079	1
1941	43[c]	898	..	2 089	1
1942	384	1 871	..	896	1 657
1943	1 150	12 395	..	282	715
1944	1 341	6 093	..	138	91
1945	266	309	11	90	16
1946	114	8	..	18	8
1947	849	2	..	65	1
1948	1 182	39	..	1 740	902
1949	509	73	225	707	646
1950	439	7	331	272	14
1951	295	152	1	469	2
1952	237	0	0	157	2
1953	142	0	162	251	3
1954	98	0	5	22	7
1955	2 500	0	1	72	0
1956	1 900	0	9	2 173	0
1957	1 100	128	65	1 924	41
1958	540	0	156	6	0
1959	253	0	115	23	0
1960	341	0	33	0	0
1961	96	0	17	0	0
1962	16	0	1	0	0
1963	6	0	0	0	0

[a] A horizontal line beneath a figure indicates that this represents the last probable occurrence of endemic smallpox.
[b] .. = data not recorded.
[c] Number of reported deaths.

during the period under review (Fig. 8.13), except those of the Mediterranean littoral (Fig. 8.11), is evident.

There is no generally accepted way of subdividing this large and varied continent. The descriptions of the eradication programmes in Africa follow one pattern (Chapters 17–22) and those of certification by the international commissions follow another (Chapters 25–27). The countries of the Mediterranean littoral constitute a well-defined North Africa (Fig. 8.11); while the countries south of and including Angola, Zambia, Malawi and Mozambique clearly delimit southern Africa (Fig. 8.15). The countries between these two regions have been designated as western, central and eastern Africa (Fig. 8.14).

NORTH AFRICA

The countries of the Mediterranean littoral of Africa (see Fig. 8.11) have long had more extensive contacts with other Mediterranean countries than with Africa south of the

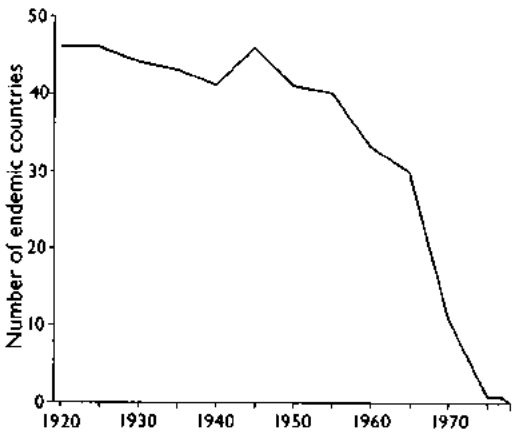


Fig. 8.13. Number of countries of the 47 in Africa in which smallpox was endemic at various times between 1920 and 1977. National boundaries as of 1982.

Sahara. Smallpox was endemic in all these countries in the first 4 decades of the century (Table 8.19). In Egypt, the most populous country of the region, smallpox was endemic but epidemics in which 2 or 3 times the usual incidence was reported occurred in 1904–1905, 1909, 1914–1915 and 1919–1920 (Table 8.20). General vaccination of the whole population was carried out in 1919 and again in 1926 in response to an epidemic that took place during that year (Ahmad, 1933). Smallpox was also reported to be very common in Algeria, Morocco, and Tunisia; Low (1918) quotes Clemow as stating that variolation by insufflation was practised in Tunisia, "often with disastrous results".

By the mid-1930s vaccination campaigns organized by the various colonial powers in the region—France, Italy, Spain and the United Kingdom—had reduced smallpox to low levels (Table 8.19). There was a severe epidemic in Egypt in 1932–1934, which did not affect the other North African countries. At the end of the 1930s endemic smallpox had been virtually eliminated in all these countries except Morocco, but the fighting and unrest associated with the Second World War led to severe outbreaks in all 5 countries, including the sparsely populated Libya. The contrast with Europe is striking (compare Tables 8.1 and 8.19); the only outbreak of smallpox in Europe associated with the Second World War (Italy, 1944–1947) was due to an importation from North Africa, whereas major epidemics occurred over a period of several years in each of the North African countries. Most of these were due to variola major, but the outbreaks in Morocco were apparently caused by variola minor (case-fatality rates, 2–3%). However, after 1948, improved health services brought about a great reduction and the eventual elimination of smallpox throughout North Africa—more slowly in Algeria, which was engaged in internal conflict, than elsewhere. This was accomplished by vaccination campaigns utilizing liquid vaccines.

WESTERN, CENTRAL AND EASTERN AFRICA

These regions comprise a large area lying between latitudes 22°N and 12°S, and include some 30 countries (Fig. 8.14). During the first part of the 20th century most of these countries were administered as colonies, by several European powers—Belgium, France, Germany (until the First World War) and the United Kingdom. They became independent countries mostly during the late 1950s and early 1960s. Smallpox was endemic in the majority of them throughout the 1960s and in Ethiopia and Somalia until the mid-1970s.

Western Africa

The reported incidence of smallpox in selected countries of this region is shown in Table 8.21. Reporting was unsatisfactory except in the major towns, but there did not seem to have been much diminution in the incidence of smallpox during the 20th century up to the time of independence, except in some of the French colonies.

More detailed accounts exist of the severity of smallpox in particular colonies and countries. Külz (1905) suggested that at the beginning of the 20th century the annual mortality from smallpox in Togoland (then a German colony) amounted to as much as 1% of the population.

The situation in French West Africa has been described by Breman et al. (1977a). The Federation of French West Africa was formed in 1904, and shortly after this the French authorities reported smallpox in several territories of the Federation. A vaccine production centre was established at Kindia in Guinea in 1905, and from 1909 onwards a more stable dried vaccine was used (Fasquelle & Fasquelle, 1971). As surveillance improved the completeness of reporting increased; case-fatality

Table 8.19. North Africa: numbers of reported cases of smallpox, 1920–1964[a,b]

	Egypt	Morocco	Algeria	Tunisia	Libyan Arab Jamahiriya
Population (millions) 1960 population (millions)	13 (1920) 26	8 (1939) 12	6 (1921) 11	3 (1946) 4	1 (1954) 1
1920	3 021	558	1 172	..	..
1921	93	203	755	..	..
1922	309	879	184	..	..
1923	519	551	141	279	..
1924	799	330	483	606	69
1925	762	471	1 747	1 270	77
1926	2 676	851	2 473	188	29
1927	240	1 292	4 336	101	7
1928	20	254	383	101	3
1929	26	280	191	138	0
1930	14	219	30	59	0
1931	10	727	21	18	7
1932	609	1 575	17	2	2
1933	5 691	112	14	5	0
1934	1 344	55	19	3	0
1935	165	42	19	7	0
1936	3	40	101	3	0
1937	1	23	15	13	0
1938	1	26	13	0	0
1939	0	16	6	2	9
1940	2	115	11	0	..
1941	0	1 961	1 029	0	..
1942	0	2 081	1 164	1	0
1943	4 138	1 173	1 855	4	6
1944	11 194	796	1 188	19	89
1945	1 355	2 700	334	190	104
1946	416	2 055	565	797	1 450
1947	170	93	533	1 224	2 400
1948	16	29	422	534	236
1949	3	14	314	1	0
1950	9	18	146	2	0
1951	2	7	102	5	0
1952	0	11	86	7	0
1953	0	0	56	7	1
1954	0	0	67	1	51
1955	0	2	73	0	0
1956	0	0	18	2	0
1957	1	0	8	0	2
1958	0	0	15	0	0
1959	30	0	11	0	0
1960	0	0	7	0	0
1961	0	0	8	0	0
1962	0	0	1	0	0
1963	0	0	5	0	0
1964	0	0	0	0	0

[a] A horizontal line beneath a figure indicates that this represents the last probable occurrence of endemic smallpox.
[b] .. = data not recorded.

rates in French West Africa as a whole varied between 6% and 20%. Variola minor appears to have occurred without concurrent variola major in Guinea in 1939 and 1940, and again in 1959 1961. Otherwise the data suggest that both variola major and variola minor occurred at some time each year in some part of the Federation.

Fasquelle & Fasquelle (1971) have described the eradication programme that was mounted in Côte d'Ivoire in 1961, the year after it became independent. The objective was achieved by mass vaccination, using French-type freeze-dried vaccine. In a population of 3.8 million, 2.4 million vaccinations were carried out in 1961 and 3.7 million by 1963. The routine was established of primary vaccination during the first year of life and revaccination at school age and again at the age of about 18 years. The incidence of smallpox fell rapidly, elimination being achieved in 1966.

Table 8.20. Egypt: numbers of reported cases of and deaths from smallpox, 1886–1931[a]

Year	Number of cases	Number of deaths
1886	416	264
1887	509	271
1888	416	181
1889	1 281	861
1890[b]	1 193	498
1891	623	202
1892	1 669	544
1893	821	313
1894	505	155
1895	1 723	358
1896	2 811	945
1897	2 580	846
1898	1 619	467
1899	1 724	431
1900	2 690	485
1901	2 221	530
1902	1 220	243
1903	2 357	565
1904	4 336	1 093
1905	4 186	851
1906	1 965	409
1907	2 130	573
1908	2 578	620
1909	4 096	1 023
1910	3 117	648
1911	2 824	737
1912	1 985	456
1913	2 934	706
1914	7 097	1 564
1915	5 222	1 262
1916	2 972	902
1917	1 567	409
1918	1 198	306
1919[c]	7 895	1 926
1920	3 021	796
1921	93	24
1922	309	89
1923	519	145
1924	799	221
1925	762	158
1926[c]	2 676	542
1927	240	34
1928	20	4
1929	26	4
1930	14	0
1931	10	0

[a] Based on Ahmad (1933).

[b] In 1890 a law was introduced requiring the vaccination of every newborn infant before the age of 3 months. It was amended in 1897 and 1917, but not enforced.

[c] General vaccination of the whole population (i.e., vaccination and revaccination) was carried out in these years.

Central Africa

The countries included in this somewhat arbitrary grouping are Burundi, the Central African Republic, Chad, Rwanda, the Sudan, Uganda and Zaire. The incidence of smallpox in the most heavily populated of these countries during the period 1920–1966 is shown in Table 8.22. The Sudan and Zaire are the two largest countries in Africa and have strongly contrasting climates, much of the Sudan being semi-desert, while Zaire includes the largest area of tropical rain forest in Africa. The Sudan was under Anglo-Egyptian control until 1955 and became completely independent in 1956. Zaire was a Belgian colony from 1908 until 1960, when it gained independence and became the Democratic Republic of the Congo, changing its name to Zaire in 1971.

Sudan

The smallpox situation in the Sudan has been described in some detail by Bayoumi (1974) and Hartwig (1981). The largest country in Africa, the Sudan was located at a major crossroads for smallpox transmission, being continually exposed to the introduction of smallpox from Egypt by way of the traffic on the Nile, from West Africa through groups of pilgrims crossing the country to and from Mecca (Bayoumi, 1972), and from Ethiopia in the east.

Records of reported cases of smallpox go back to 1925 (Bayoumi, 1974; see Table 8.22), all parts of the country being affected. Variola minor was endemic in the south and east, where the Sudan borders on Zaire, Uganda and Ethiopia, and there were repeated importations of variola major from the west, brought in by the large numbers of pilgrims and immigrants from western Africa and other central African countries. From time to time these produced sporadic outbreaks, mainly during the dry season, when maximum population movement usually occurred.

There was a severe epidemic of variola major extending from 1927 until 1931, apparently introduced by Ethiopian migrants. An extensive outbreak of variola minor occurred in the south between 1932 and 1934, but this did not cause nearly as much concern to medical administrators as did the periodic outbreaks of variola major along the pilgrim route and in the Gezira Irrigation Scheme (Bayoumi, 1974). Extensive vaccination campaigns, performed almost yearly in one or more provinces, reduced the incidence, and from 1941 to 1946 the reported incidence was under 250 cases a year. In 1947, scattered epidemics developed and continued until the end of the 1940s along the major lines of communication in Kordofan, Blue Nile and Kassala provinces, predominantly of variola minor, but with sporadic outbreaks of variola major. The incidence declined substantially in the mid-1950s, although there was a serious

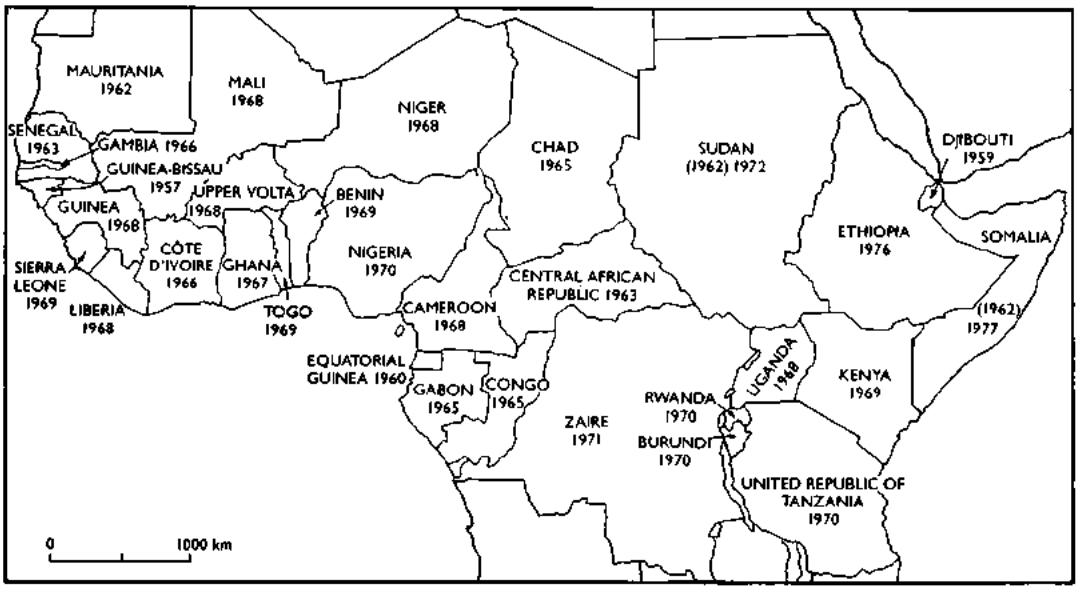


Fig. 8.14. Western, central and eastern Africa: year in which smallpox ceased to be endemic in each country (national boundaries as of 1982). Dates in parentheses (for Somalia and Sudan) indicate the initial elimination of endemic smallpox, after which endemicity was again established before final elimination in the year shown.

outbreak in Equatoria Province in 1954, and outbreaks which were probably still occurring among nomads and pilgrims were rarely reported. Endemic smallpox was eliminated in 1962, but was re-established in 1967 and eventually eliminated again in 1972 (see Chapter 18).

Zaire

Data on cases and deaths in the former Belgian Congo from about 1940 onwards suggest that during the 1940s variola minor was the predominant variety of smallpox in that country, and the same situation obtained

The Sudan and the Pilgrimage to Mecca

The Mecca Pilgrimage is probably the largest of all pilgrimages to a sacred place, and currently involves over a million pilgrims assembling at the holy places in Saudi Arabia over a period of a few days, at a fixed date in the Hegira year. The Sudan, of which the northern and central parts are inhabited by Muslims, is at the crossroads of the passage of pilgrims from the large Islamic populations in western Africa to Mecca. They came, and come, by all kinds of transportation from western Africa through Chad to cross the ill-defined border of some 900 kilometres into the provinces of Darfur and Kordofan. Within the Sudan, they often stop to work in the Gezira, and then go on by road or railway to Port Sudan, whence they cross the Red Sea by boat to Saudi Arabia. In the 1920s a quarantine station was established at Geneina, on the Sudan–Chad border, but many pilgrims evaded it. Outbreaks of variola major in nothern Sudan in 1927, 1929, 1949, 1951–1952 and 1952–1953 were attributed to entries by this route, and the disease subsequently moved westwards along the pilgrim route (Bayoumi, 1972). Later, more elaborate precautions were taken in Saudi Arabia to control the entry and dissemination of disease by pilgrims coming from all parts of the world (see Chapter 27).

Table 8.21. Western Africa: numbers of reported cases of smallpox in selected countries, 1920–1966[a]

	Nigeria	French West Africa[b]	Cameroon	Ghana	Sierra Leone	Liberia	Togo
Population (millions)	33 (1950)	19 (1950)	3 (1939)	2 (1920)	2 (1946)	1 (1950)	0.7 (1922)
1960 population (millions)	42	25	6	7	2	1	1.5
1920	..	..	..	300	6	..	..
1921	1 031	..	..	..	..	..	..
1922	..	..	..	..	44	..	..
1923	1 222	..	..	13	18	..	..
1924	119	..	..	153	2	..	..
1925	1 932	1 595	32	1 468	6	..	3
1926	847	767	85	883	..	..	2
1927	4 483	3 009	138	57	16	..	5
1928	3 695	2 319	120	8	1	..	42
1929	3 216	1 586	32	184	6	..	78
1930	5 119	4 084	185	185	2	..	66
1931	2 315	1 810	265	278	6	..	11
1932	9 464	1 850	492	12	998	..	7
1933	12 601	2 635	475	1	2 378	..	7
1934	10 389	2 296	463	48	2 333	274	19
1935	5 498	4 691	138	0	1 981	..	3
1936	4 883	3 909	1 061	59	565	104	33
1937	3 675	3 128	20	43	134	..	0
1938	7 511	2 348	271	123	55	..	29
1939	4 967	2 353	82	389	52	..	301
1940	3 298	1 620	1	77	29	..	13
1941	1 097	980	0	1 470	7	..	1
1942	2 514	2 007	3	2 025	8	..	0
1943	6 496	7 584	242	20	3	..	0
1944	4 958	4 787	1 063	143	484	..	174
1945	5 576	7 442	931	702	650	..	535
1946	7 620	7 734	106	1 646	750	87	470
1947	5 425	7 821	139	848	465	14	65
1948	5 746	2 713	7	1 269	200	0	107
1949	14 863	1 890	55	91	157	5	152
1950	20 948	3 542	163	353	40	0	147
1951	11 879	4 046	721	478	34	0	190
1952	9 264	7 254	1 106	695	36	..	628
1953	3 258	4 659	63	865	12	..	228
1954	6 417	3 764	197	79	5	..	226
1955	5 780	3 958	42	59	49	..	2
1956	4 798	5 948	42	251	946	..	6
1957	9 733	12 693	4	154	4 846	230	9
1958	1 808	6 676	5	161	513	1 717	44
1959	1 599	5 751	17	104	96	1 869	66
1960	4 140	6 107	0	139	12	136	347
1961	3 600	10 890	1 145	70	6	1 116	281
1962	3 864	9 602	743	145	78	325	571
1963	1 778	2 868	135	23	14	88	285
1964	1 430	2 329	88	9	90	258	34
1965	4 566	1 372	28	7	60	40	13
1966	4 953	2 005	2	13	293	32	201

[a] .. = data not recorded.
[b] Comprising present-day Benin (formerly Dahomey), Burkina Faso (formerly Upper Volta), Côte d'Ivoire, Guinea, Mali, Mauritania, Niger and Senegal.

in the former trust territory of Ruanda-Urundi (now Rwanda and Burundi). However, in most years outbreaks of variola major and variola minor occurred, usually in different parts of the area. After 1960 variola major appeared to predominate (see Chapter 18). Liquid glycerolated vaccine was prepared in the colony's own laboratories, but the Belgian authorities reported great difficulties in distributing potent vaccine. The take rate in primary vaccinations during 1938–1946 varied between 8.8% and 74.3%, with an average for the 9 years of 37.6% (Tulloch, 1980). Many cases of smallpox, including variola minor, were reported in subjects who were supposed to have been vaccinated (Fabre, 1948). Endemic smallpox was not eliminated until 1971.

Table 8.22. Central Africa: numbers of reported cases of smallpox in selected countries, 1920–1966[a,b]

	Belgian Congo (Zaire)	Sudan	Ruanda-Urundi[c]	Uganda	Chad
Population (millions)	7 (1921)	9 (1950)	3 (1935)	5 (1946)	3 (1950)
1960 population (millions)	18	11	6	7	3
1920	507	..	..	..	..
1921	1 497	..	..	506	..
1922	1 040	..	..	104	..
1923	1 956	..	..	97	..
1924	2 371	..	..	7	..
1925	781	0	3	13	..
1926	9 140	63	14	6	..
1927	2 980	218	7	17	..
1928	1 337	2 402	2	1	9
1929	1 343	6 467	3	32	..
1930	1 497	2 179	72	2	139
1931	1 241	218	481	0	20
1932	2 270	47	77	0	25
1933	3 417	228	22	0	129
1934	3 253	173	62	0	42
1935	2 574	72	30	2	14
1936	2 873	577	71	32	32
1937	3 792	425	129	0	12
1938	3 269	527	67	0	28
1939	6 495	553	240	0	1 208
1940	6 394	515	26	10	590
1941	4 614	46	53	32	1 067
1942	2 658	12	55	0	3
1943	4 257	182	18	128	198
1944	2 148	242	2 201	4 737	2 388
1945	6 350	0	848	1 558	1 670
1946	4 122	62	76	581	243
1947	2 756	917	447	389	41
1948	2 950	1 438	147	254	12
1949	2 218	250	43	47	400
1950	4 591	110	484	5	460
1951	2 524	346	571	43	495
1952	2 832	3 670	819	243	2 789
1953	4 699	3 030	219	341	680
1954	5 214	4 200	234	199	518
1955	6 217	1 427	113	101	259
1956	4 663	25	58	231	51
1957	1 950	295	34	477	54
1958	1 181	380	29	360	15
1959	3 035	336	77	334	17
1960	1 408	162	12	740	2
1961	3 624	8	8	400	502
1962	3 775	95	54	631	769
1963	5 523	0	11	419	10
1964	3 262	0	0	510	5
1965	3 783	69	1 218	1 351	73
1966	1 913	0	363	614	0

[a] A horizontal line beneath a figure indicates that this represents the last probable occurrence of endemic smallpox.
[b] .. = data not recorded.
[c] From 1962, the two separate states of Rwanda and Burundi.

Uganda

Prior to the First World War, the main sources of smallpox were the caravans of Arab and other traders. Between 1914 and 1920 over 20 000 deaths from smallpox were reported in Uganda, the overall case-fatality rate among cases treated in government hospitals between 1911 and 1923 being over 23%. Following extensive vaccination, only a few outbreaks were reported between 1920 and 1944, when the outbreak of variola minor that had started in Kenya in 1943 spread to Uganda, producing 4737 reported cases in 1944, and then gradually declined. Small outbreaks, one of which, in 1956, was due to variola major, continued every year until endemic transmission ceased in 1968.

Eastern Africa

This grouping of countries includes Ethiopia, Kenya, Somalia and the United Republic of Tanzania, former colonies of European powers which became independent in the 1950s and early 1960s. Smallpox appears to have been common in the early part of the 20th century and case-fatality rates were usually between 20% and 30% (Low, 1918). Table 8.23 sets out the reported annual incidence of smallpox in these countries from 1920 to 1966. As elsewhere in Africa, the figures provide an index of the incidence but it is certain that there was gross under-reporting.

Ethiopia and Somalia

It is difficult to obtain reliable information on smallpox in Ethiopia before the Intensi-

Table 8.23. Eastern Africa: numbers of reported cases of smallpox in selected countries, 1920–1966[a]

	Ethiopia	Tanganyika[b]	Kenya	Somalia
1946 population (millions)	16 (1950)	7	5	2
1960 population (millions)	20	10	8	2
1920	..	7	217	..
1921	..	1 427	200	..
1922	..	567	..	..
1923	..	453	108	..
1924	..	40	1	..
1925	..	1 391	278	..
1926	..	75	4	..
1927	..	234	29	..
1928	..	28	5	3
1929	..	182	1	121
1930	..	4 547	30[c]	122
1931	41	1 746	0	13
1932	36	768	0	14
1933	7	629	3	114
1934	4	411	1 800	91
1935	27	503	15	245
1936	276	1 649	1	162
1937	459	1 462	200[c]	50
1938	31	1 095	0	3
1939	201	599	0	78
1940	164	156	0	3
1941	0	92	0	..
1942	1	90	0	..
1943	7	201	3 551	634
1944	11	5 735	3 372	13
1945	13	12 283	764	1
1946	4	12 672	824	3
1947	65	2 960	479	0
1948	43	1 206	133	0
1949	15	1 045	45	0
1950	62	6 416	10	+
1951	44	854	4	+
1952	80	373	0	+
1953	178	1 200	0	248
1954	834	928	14	1 555
1955	2 662	542	101	641
1956	2 832	605	660	84
1957	1 408	856	1 108	91
1958	1 604	1 204	796	0
1959	990	1 442	572	94
1960	1 518	1 584	397	47
1961	2 586	1 002	289	36
1962	551	1 074	95	221
1963	733	836	249	0
1964	300	1 461	273	0
1965	124	2 762	276	0
1966	358	3 027	159	2

[a] .. = data not recorded; + = smallpox present, but number of cases unknown.
[b] In 1964, combined with Zanzibar and Pemba to form the United Republic of Tanzania.
[c] The last probable occurrences of endemic smallpox.

fied Smallpox Eradication Programme began work there in 1971, when only variola minor was present and was very poorly reported (see Chapter 21). Early in the century smallpox caused devastating outbreaks, and just before the First World War about 20% of the population of the province of Shewa (in which Addis Abeba is situated) were said to be pockmarked (Pankhurst, 1965). Extensive vaccination campaigns were undertaken by Italian health officials after the Italian occupation of the country in 1936, vaccine being produced in Addis Abeba. Murray (1951) was unable to comment on smallpox in Ethiopia, except to say that "a small but steady incidence" occurred in Shewa Province. Teclemariam (1965) reported that an epidemic of smallpox with a high case-fatality rate took place in the Shewa area in 1960 and a smaller outbreak occurred in 1964, but Herrlich et al. (1963) reported experiments with a strain of "alastrim virus" recovered during an epidemic in Ethiopia in 1958. Variola minor appears to have completely replaced variola major throughout Ethiopia before 1971, and was finally eliminated in 1976.

In the colonies that eventually became Somalia, Low (1918) reported that epidemics of variola major occurred in the early years of the century, mainly in the larger towns when fairs were held. By the late 1940s endemic smallpox had been eliminated from the Somaliland Protectorates, but outbreaks occurred following importations during the mid-1950s. This pattern continued, and the last major outbreak of smallpox in the world occurred in Somalia in 1976–1977, following importations from Ethiopia.

Kenya and the United Republic of Tanzania

Prior to the First World War the prevalence of smallpox in the two colonies of Kenya and Tanganyika was lower than in the 19th century. Vaccination was introduced in the larger towns, but outbreaks of variola major, with case-fatality rates of 25–30%, occurred sporadically. From the mid-1930s onwards variola minor occurred from time to time and because it was so much milder than variola major proved considerably more difficult to control (Conacher, 1957).

The situation in Kenya has been documented somewhat more fully than in many other African countries, but is characteristic of the situation in a large number of them. There was a severe famine in central Kenya in 1897–1900, due to a combination of drought, pleuropneumonia and rinderpest among the cattle, and a locust plague. Dawson (1979) has drawn attention to the way in which extensive movements of the population in quest of food created the conditions for the severe outbreak of smallpox that occurred in 1899. Subsequently, the social changes accompanying European colonization changed the pattern of smallpox in Kenya, as in other African colonies.

The production of smallpox vaccine, using seed virus obtained from India, began in Nairobi in the first decade of the century. Trade expanded with the introduction of cash crops, labour migration caused larger and more frequent population movements and urbanization created larger and denser populations—all of which increased the opportunities for the transmission of smallpox. On the

Special Relations between Eastern Africa and India

Throughout history, Arab dhows and ships from India have traded with the ports on the east coast of Africa. During the early days of British colonization in Africa indentured labourers were brought from India to assist in large-scale agricultural production in Natal (South Africa), Kenya, Uganda and Tanganyika. The Indian indentured labourers soon established themselves as shopkeepers throughout these colonies and active communications were maintained between them and their relatives in India. This traffic had a significant influence on the incidence of smallpox in eastern Africa, especially in Kenya and Tanganyika, and to a lesser extent in Natal, variola major ("Asiatic smallpox") being repeatedly imported into all three areas from India.

other hand, vaccination, though ineffective as a general public health measure because of poor vaccine and inadequate funding, was used effectively to control outbreaks of variola major, so that smallpox appeared in frequent local outbreaks with very occasional widespread epidemics. A notable example of the latter occurred in 1916, when survivors of the Carrier Corps (a contingent of Kenyan Africans who acted as army porters during the British invasion and conquest of German East Africa (Tanganyika)) were returned from Nairobi to their home districts regardless of their medical condition. The result in one province, repeated in many others, was 100 separate outbreaks of smallpox, as well as other diseases (Dawson, 1979).

The production of vaccine in Nairobi was greatly expanded in the 1930s to supply most of the British colonies in eastern Africa. Variola major was imported into Mombasa from India on several occasions during the 1920s and 1930s, but endemic smallpox was eliminated from Kenya in 1930. In 1934 variola major was introduced again from the north, by nomadic Somalis (Seymour-Price et al., 1960). A widespread epidemic occurred but the disease was eliminated in 1936, only to be reintroduced by refugees from Ethiopia in 1937. No cases were reported in 1938–1942. In 1943 an epidemic of variola minor occurred, to be followed by an explosive epidemic of variola major in 1945. Subsequently, variola minor continued at a low level throughout the early 1950s, but it spread widely during the disturbances associated with Kenya's struggle for independence in 1956–1958.

Smallpox was eventually eliminated from Kenya in 1969 and from the United Republic of Tanzania in 1970.

SOUTHERN AFRICA

The countries included in this region are shown in Fig. 8.15. Table 8.24 sets out the reported incidence of smallpox in each of them between 1920 and 1966.

Angola and Mozambique

These former Portuguese territories, on the Atlantic and Indian Ocean shores of southern Africa, became independent in 1975. In relation to their experience of smallpox, they had more in common with each other than with neighbouring British colonies. Both variola major and variola minor were present during the 1940s, but the latter eventually predominated. The Portuguese promoted vigorous vaccination campaigns, using locally produced vaccines, and had eliminated smallpox from Angola by 1959, and from Mozambique by 1969.

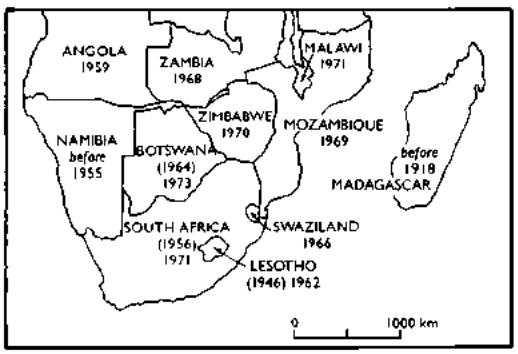


Fig. 8.15. Southern Africa: year in which smallpox ceased to be endemic in each country (national boundaries as of 1982.) The dates in parentheses (for Botswana, Lesotho and South Africa) indicate the initial elimination of endemic smallpox, after which endemicity was again established before final elimination in the year shown.

Malawi, Zambia and Zimbabwe

These three former British colonies had rather similar histories, typified by Zambia, in which the picture between 1920 and 1950 was one of a reduction in the incidence of variola major in the late 1930s, followed by sporadic cases of variola minor in 1940–1943, rising to a major epidemic of 6354 cases with 28 deaths in 1945. The incidence of variola minor then declined, but there was an outbreak of variola major in the Zambesi valley in 1948, with 671 reported cases and 212 deaths. Very few cases were recorded in 1949–1951, but the incidence then increased, and there was an epidemic with over 3500 reported cases in 1955. Both varieties of smallpox persisted until the disease was eliminated in 1968.

South Africa and Adjacent Countries

South Africa, the two small enclaves of Lesotho and Swaziland, and neighbouring Botswana and Namibia (formerly (German)

Table 8.24. Southern Africa: numbers of reported cases of smallpox in selected countries, 1920–1966[a,b]

	South Africa	Mozambique	Angola	Madagascar[c]	Nyasaland (Malawi)	Southern Rhodesia (Zimbabwe)	Northern Rhodesia (Zambia)
1920 population (millions)	7	4 (1932)	3	3	1.2	0.9	0.9
1960 population (millions)	18	7	5	5	4	4	3
1920	1 036	..	..	..	..	..	..
1921	1 108	..	..	0	..	515	..
1922	713	..	..	0	..	501	..
1923	285	..	..	0	14	16	59
1924	346	..	..	0	..	2	258
1925	71	..	..	25	0	12	98
1926	115	..	..	6	0	1	305
1927	60	1 292	174	15	11	7	1 241
1928	51	42	67	11	20	255	4 042
1929	53	345	95	10	1 092	427	3 856
1930	63	75	1 107	5	4 762	696	3 400
1931	28	454	1 408	21	7 414	44	152
1932	19	34	848	0	4 106	40	61
1933	24	484	371	0	3 412	80	179
1934	23	681	693	1	814	41	23
1935	21	415	406	0	170	1	32
1936	24	513	640	..	190	17	96
1937	306	286	198	..	94	246	27
1938	521	239	451	0	9	1 864	59
1939	408	638	465	0	44	223	20
1940	681	412	1 100	0	74	255	9
1941	1 014	240	1 650	0	6	87	3
1942	1 781	144	473	0	0	0	10
1943	1 469	72	652	0	13	0	124
1944	1 046	81	80	0	1	1	355
1945	3 317	220	129	0	202	33	6 354
1946	1 271	99	198	0	968	181	490
1947	1 469	29	288	0	2 583	685	98
1948	271	384	605	0	4 830	1 823	671
1949	923	374	510	0	1 264	861	20
1950	1 635	384	621	0	295	1 034	28
1951	1 434	166	236	0	122	456	10
1952	80	358	191	0	7	87	166
1953	14	394	138	0	6	11	693
1954	7	28	135	0	5	1	1 024
1955	27	31	122	0	28	157	3 538
1956	4	94	113	0	248	153	576
1957	0	32	11	0	320	34	459
1958	0	67	138	0	196	90	210
1959	0	44	7	0	559	133	178
1960	65	14	0	0	795	12	350
1961	8	91	0	0	1 465	3	233
1962	103	69	23	0	634	15	210
1963	254	102	50	0	455	38	1 881
1964	302	243	1	0	720	200	2 214
1965	191	115	0	0	226	40	528
1966	256	19	3	0	88	35	63

[a] .. = data not recorded.
[b] A horizontal line beneath a figure indicates that this represents the last probable occurrence of endemic smallpox.
[c] Endemic smallpox was eliminated during the First World War.

South West Africa) had similar experiences of smallpox, modified in each by population density, as well as the volume of international traffic—and thus the risk of importations—from other parts of Africa and from the Indian subcontinent.

The situation can be exemplified by South Africa, through which severe epidemics of variola major swept in the 18th and 19th centuries, usually after importations from India into Cape Town. After the last large epidemic in 1881, vaccination was made compulsory in the Cape Colony, a law which was extended throughout the Union of South Africa in 1919. Since the latter part of the 19th century it had been recognized that in addition to this severe disease, against which vigorous action was taken by the public health authorities, there was endemic among the black population a very mild form of

smallpox, "amaas", which today is classified as variola minor. From the turn of the century onwards, variola minor persisted in South Africa as an endemic disease, which was greatly underreported. Superimposed on this background, outbreaks of variola major occurred from time to time, especially during the First and Second World Wars.

Immediately after the First World War, an epidemic of variola minor occurred (over 1000 reported cases in both 1920 and 1921); then the reported morbidity fell to very low levels between 1927 and 1936. After that smallpox became more frequent, especially in the Transvaal, and in 1940 and 1941 epidemics of variola minor occurred in several places, probably because of the movement of the black population in connection with wartime activities. In 1943, variola major occurred in Natal, probably after an importation via a mule ship returning from India, and spread throughout that province and into the Transvaal. Whites as well as blacks were affected and the case-fatality rate was high (30% in 1945), although the case-fatality rate pertaining to both forms of smallpox for that year was only 5%. Vaccination was made compulsory, a vigorous vaccination campaign was launched and the epidemic came to an end in 1947. The annual case-fatality rates observed thereafter in different provinces, which were often between 4% and 10%, were usually calculated from a combination of cases and deaths due to both varieties of smallpox; sometimes there were "pure" epidemics of variola major, with case-fatality rates of 39% (Natal, 1951), 23% (Transvaal, 1952) and 20% (Cape Province, 1964). Only 2 deaths were recorded among the 948 cases of smallpox reported between 1965 and 1971, when the last endemic case was notified.

Madagascar

The main point in including Madagascar in this historical survey is to emphasize the relative ease with which smallpox was controlled on an island off the coast of Africa, compared with the problem in countries of similar size and with comparable health services on the mainland. According to Coulanges (1977) variola major was once endemic in Madagascar and periodically there were severe epidemics from infection introduced from Africa or India, as in 1901, when 262 cases (with 98 deaths) were reported. Vaccine production was begun in Antananarivo in 1899 and compulsory vaccination and revaccination were instituted in 1909. Favoured by its geographical isolation, Madagascar was the first country in Africa to eliminate smallpox. This was achieved during the First World War, after which there were no further cases of smallpox in Madagascar, except for a few imported cases each year between 1925 and 1931.

SMALLPOX IN OCEANIA DURING THE 20TH CENTURY

Apart from some widespread outbreaks among the aborigines of Australia during the 19th century, all of which died out after a few years (see Chapter 5), smallpox never became established as an endemic disease in Australia, New Zealand or the islands of the Pacific Ocean. From the beginning of the 20th century they were well protected from importations by their geographical remoteness and the effective quarantine measures imposed on visiting shipping. This situation led to a disregard for infantile vaccination, which by the early years of the 20th century had reached a very low level in Australia and New Zealand.

Nevertheless, a long-standing requirement for valid vaccination certificates for all travellers, combined with vigilant seaport and, later, airport medical inspections and quarantine, kept both Australia and New Zealand free of serious outbreaks of smallpox, except for separate importations of alastrim into each country in 1913.

Australia

The Australian epidemic of alastrim was initiated in April 1913 by a ship's steward who was infected in Vancouver, Canada, and slipped through the medical inspection in Sydney (Cumpston & McCallum, 1925). The outbreak which followed lasted until December 1917 and produced 2400 cases in various parts of Sydney and in country towns in New South Wales, but only a minor extension into one other state—Queensland. It was of very low virulence, with only 2 deaths attributable to smallpox, and of low infectivity, spreading slowly in a largely unvaccinated population of 1.8 million. Control was achieved by vaccination and the segregation of cases and contacts. Subsequently a few very small outbreaks

of both variola major and variola minor occurred, but the effectiveness of the quarantine arrangements was indicated by the fact that, between 1909 and 1923, 40 ships were quarantined for smallpox or suspected smallpox.

New Zealand

The New Zealand epidemic was introduced by a Mormon missionary in April 1913 and lasted about a year. Among people of European origin, there were 114 reported cases, with no deaths, but among the Maoris—the indigenous Polynesian people—there were 1778 reported cases and 55 deaths. Although cases among the Maoris were probably underreported, Dixon (1962) noted that some cases of variola minor were very severe in this population group, which had never before been exposed to smallpox.

Hawaii

Situated at the crossroads of the Pacific, Hawaii was frequently visited by ships with

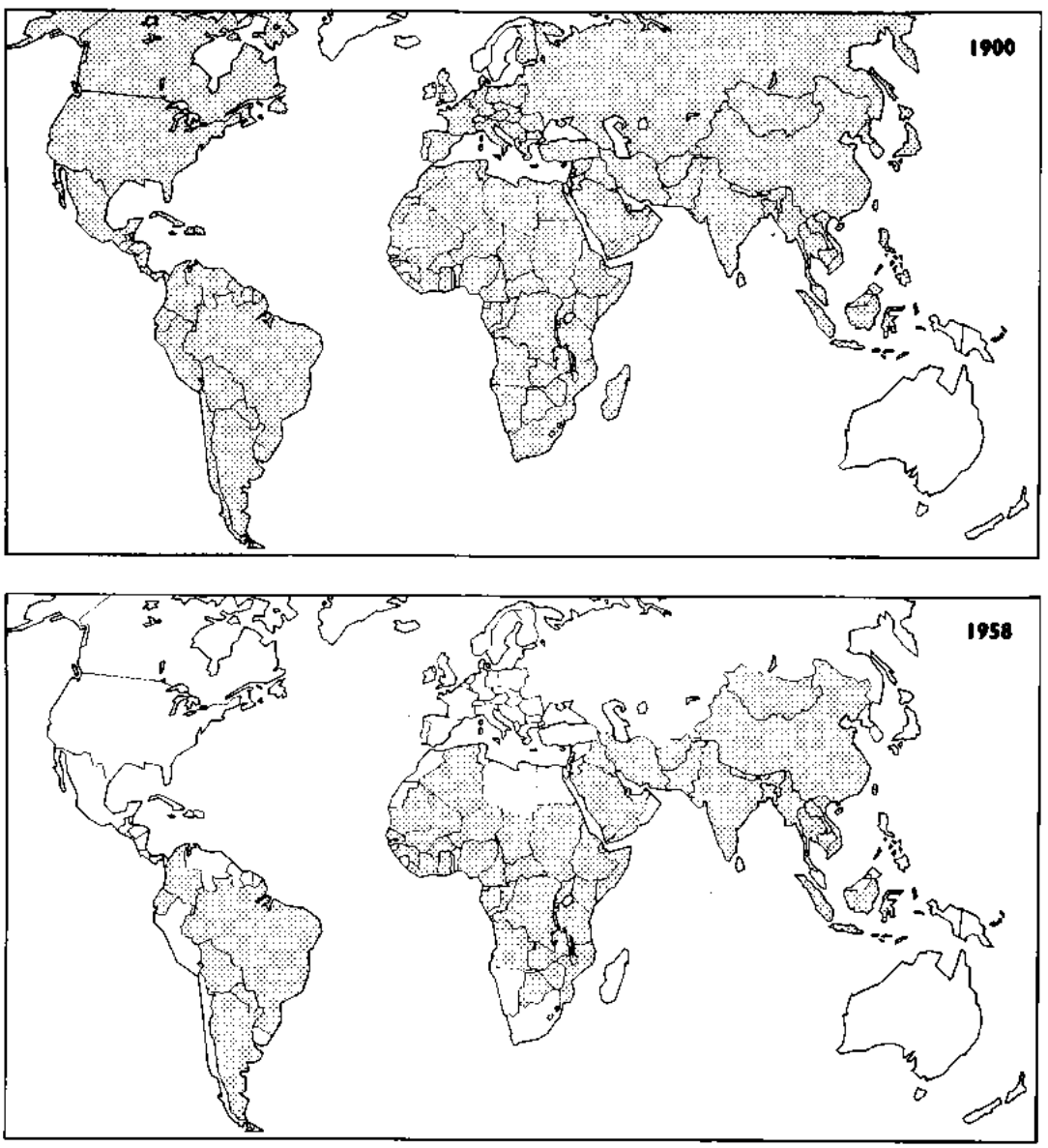


Fig. 8.16. Countries in which smallpox was endemic in 1900 and in 1958.

smallpox patients on board, especially during the early years of the century. For example, there were 5 cases on 4 ships in 1903, 3 cases on 1 ship in 1906, 8 cases on 1 ship in 1907, 5 cases on 3 ships in 1908 and 16 cases on 8 ships in 1910. Most of these ships came from ports in eastern Asia, but occasionally a ship from San Francisco carried a patient with variola minor, which, however, never became established on the islands. The only outbreak to occur on land during the 20th century was in the detention camp to which illegal immigrants from the Philippines were taken, and in which there were 52 cases of variola major in 1911.

SUMMARY: THE GLOBAL INCIDENCE OF SMALLPOX, 1900–1958

At the beginning of the 20th century—about a hundred years after the introduction of vaccination—smallpox was still endemic in almost every country of the world (Fig. 8.16). A few countries in Europe with small populations had eliminated the disease by vaccination, and the isolated and sparsely populated countries of Australia, New Zealand and many small islands were protected by distance and effective seaport medical inspections and quarantine.

The only variety of smallpox found in Asia was variola major, but for the first two or three decades of the 20th century endemic variola major and variola minor coexisted in many countries of Africa and North and South America, as well as in a few countries of Europe. By the 1930s variola major had been completely replaced by variola minor as an endemic disease in the USA, Canada, the United Kingdom and in several Latin American countries, but curiously not in Mexico.

In Europe, the reductions in the incidence of smallpox achieved early in the 20th century were reversed by the First World War (1914–1918), which led to a great resurgence of the disease in Russia and its spread from there to many other countries. Between the First and Second World Wars it was gradually brought under control in Europe and North America and in a few countries elsewhere but continued almost unchecked in Africa and most of Asia, where any gains made were lost during and just after the Second World War. This latter conflict had virtually no influence on the incidence of smallpox in Europe and North America.

After the Second World War data collection by the World Health Organization gave a better picture of the global scene. Both Europe and North America were free of endemic smallpox in 1958 (Fig. 8.16). Significant advances were also made in some countries of Asia and in Central and South America. During the 1950s smallpox was eliminated from most countries of the Mediterranean littoral of Africa. Elsewhere in Africa it remained endemic—variola major in some places, variola minor in others, and both concurrently in many countries. Smallpox was eliminated from China and several other countries of eastern Asia during the 1960s, but on the Indian subcontinent variola major remained a widespread and severe endemic disease.

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CHAPTER 9

DEVELOPMENT OF THE GLOBAL SMALLPOX ERADICATION PROGRAMME, 1958–1966

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THE COMMITMENT TO GLOBAL SMALLPOX ERADICATION, 1958–1959

The decision by the Twelfth World Health Assembly, in May 1959, to undertake the global eradication of smallpox marked the beginning of a programme which, some 18 years later, would witness the last naturally occurring case. The Health Assembly's policy, which made the global eradication of a disease one of WHO's goals, was not without precedent, a similar decision with regard to malaria having been taken 4 years before.

The commitment to smallpox eradication in 1959 represented, for the Health Assembly, an abrupt reversal of its views regarding the disease. The problem of smallpox and its control had been the subject of discussions in the Health Assembly in 1950, 1953, 1954 and 1955. An eradication programme had been proposed, in fact, by the first Director-General, Dr Brock Chisholm, to the Sixth World Health Assembly in 1953. However, after 2 years of study and debate, the Eighth World Health Assembly, in May 1955, rejected the concept as unrealistic, and the terse resolution which was adopted (WHA8.38) simply urged "that health administrations conduct, wherever necessary, campaigns against smallpox as an integral part of their public-health programmes" (World Health Organization, 1973a).

From 1955 to 1958, the issue of smallpox eradication lay dormant but, at the Eleventh World Health Assembly, Professor Viktor Zhdanov, Deputy Minister of Health of the USSR and a delegate to the Health Assembly, presented a formal, lengthy report which argued that the problem of smallpox was an important one for endemic and non-endemic countries alike, that eradication was theoretically feasible and that national programmes had demonstrated it to be a practicable possibility (World Health Organization, 1958a). The report concluded: "As regards its complete eradication throughout the world, we think that this can be achieved within the next ten years." No reference was made to an 8-year-old regional programme for smallpox eradication in the Americas nor to the Health Assembly's earlier discussions on smallpox. The USSR had not participated in those discussions, however, having withdrawn from active participation in WHO from 1948 to 1957.

The new initiative originated with Professor Zhdanov himself. From 1951, when he had first assumed responsibility for communicable disease control in the USSR, as Chief of the Department of Sanitary and Epidemiological Services, he had taken an active interest in the concept of disease eradication. His interest was stimulated, in part, by the successful interruption of smallpox transmission throughout the USSR in 1936, and by the elimination of dracunculiasis from the Central Asian republics of the USSR following a 10-year campaign that ended in 1932 (Isaev, 1956; Litvinov, 1970). These successes led him to initiate a study of infectious diseases in the Soviet Union for the purpose of identifying others which might similarly be eliminated (Zhdanov & Timakov, 1952). By assigning more resources in the short term to disease elimination, longer-term savings could be anticipated. Smallpox remained a problem, however, particularly in the Central Asian republics, because of importations from Afghanistan and Iran, 537 cases being recorded between 1950 and 1957 (Burgasov, 1968). Professor Zhdanov's report to the Health Assembly pointed out that the danger which endemic countries posed to others caused "the countries which are free from smallpox . . . to make considerable efforts and spend large sums on vaccinating and revaccinating the population in order to provide constant strong immunity against this disease". Smallpox, as he saw it, would be much easier to eradicate than any of the other infectious diseases, as indicated by the success of the

programme in the USSR. Despite the diverse problems presented by a country so large and abundantly populated, transmission had been stopped by means of a programme of compulsory vaccination (Vasil'ev & Vasil'ev, 1982). For other countries to do likewise seemed both logical and feasible and the USSR was willing to offer its assistance to support such efforts. In addition to offering 25 million doses of vaccine to WHO, it informed the Director-General at the twenty-third session of the Executive Board that it had sent offers of assistance to Burma, Cambodia (later Democratic Kampuchea), Ghana, Guinea, India, Indonesia, Iraq and Pakistan (World Health Organization, 1959a).

The Eleventh World Health Assembly was held in Minneapolis, Minnesota (USA), and, with this venue in mind, Professor Zhdanov introduced his report with a quotation: "As early as 1806, the President of the United States of America Thomas Jefferson . . . said in his letter to Jenner: 'It is owing to your discovery . . . that in the future the peoples of the world will learn about this disgusting smallpox disease only from ancient traditions'." The Zhdanov report proposed that vaccination and revaccination campaigns should be conducted throughout the endemic areas of the world, commencing in 1959. It recommended that vaccination should be made compulsory and that freeze-dried vaccine should be used. It also suggested that the programme could be accelerated if the Leicester system were introduced as well. This system, as noted in the report, was used for outbreak control, mainly in England (see Chapter 6), and resembled what eventually came to be called surveillance–containment activities—namely, "prompt identification of the disease, special notification, isolation, quarantine, disinfection measures"—although it included the "eradication of flies" as well (Fraser, 1980).

WHO, 1958

Plate 9.1. Viktor M. Zhdanov (b. 1914), Academician and Deputy Minister of Health of the USSR, 1955–1960, proposed to the World Health Assembly in 1958 that WHO should undertake the global eradication of smallpox. Many epidemiologists whom he trained while Director of the Ivanovsky Institute served as WHO staff and consultants for the eradication of smallpox.

The draft resolution introduced by the USSR in 1958 for consideration by the Health Assembly differed from the report in suggesting that eradication in 4–5 years was possible in accordance with the following timetable: (1) preparation of the necessary amount of vaccine in 1958–1960 and the training of vaccinators; (2) vaccination during 1959–1960 of the populations in which principal endemic foci existed; and (3) completion of eradication in 1961–1962 by additional vaccination and revaccination. Nothing was said of the Leicester system in the resolution.

The concept of global eradication was broadly endorsed by virtually all the delegates who spoke, although a number believed that the timetable was too optimistic and some wondered whether there might not be insuperable technical and administrative problems. Accordingly, the resolution was altered to request "the Director-General to study and report to the Executive Board . . . on the financial, administrative and technical implications of a programme having as its objective the eradication of smallpox" (see box).

Immediately after the Health Assembly, the Executive Board met and formally accepted the gift of freeze-dried vaccine from the USSR, as well as 2 million doses of glycerolated vaccine offered by Cuba. The Board noted in resolution EB22.R12 that the Director-General would establish a special account for smallpox eradication, which would "be credited with the value, as reported by the governments concerned, of these gifts of vaccine and of any gifts for the same purpose which may be accepted by the Board

Resolution WHA11.54, adopted at the Eleventh World Health Assembly in 1958

"Noting that smallpox still remains a very widespread and dangerous infectious disease and that in many regions of the world there exist endemic foci of this disease constituting a permanent threat of its propagation and consequently menacing the life and health of the population;

"Having regard to the economic aspect of the question, which shows that the funds devoted to the control of and vaccination against smallpox throughout the world exceed those necessary for the eradication of smallpox in its endemic foci and consequently the destruction of the sources from which the infection arises and spreads, and clearly indicates that the eradication of smallpox might in future make vaccination and all expenditures involved in its application redundant;

"Taking into account the level of development reached by medical science and the health services in the control of infectious diseases, and in particular of smallpox, and the manifest tendency of the morbidity of smallpox to diminish in recent years;

"Having regard to the decisions and pertinent practical measures adopted by WHO for smallpox control and the intensification of antismallpox programmes, in particular resolutions WHA3.18, EB11.R58, WHA6.18, EB12.R13, EB13.R3, WHA7.5, WHA8.38, and WHA9.49; and

"Considering it opportune to raise the problem of the world-wide eradication of smallpox in the near future,

"1. REQUESTS the Director-General to study and report to the Executive Board at its twenty-third session on the financial, administrative and technical implications of a programme having as its objective the eradication of smallpox, the study to include the various problems involved in carrying out the following activities:
   (*a*) investigation of the means of ensuring the world-wide eradication of smallpox, taking into account the fact that smallpox persists in certain areas despite repeated vaccination campaigns;
   (*b*) encouragement of the preparation during 1958–1960 of the necessary amount of smallpox vaccine in national laboratories and institutes;
   (*c*) training of vaccinators among the local population in countries in which mass immunization campaigns will be conducted;
   (*d*) the pooling of experience and the formulation of recommendations for the production of a sufficient amount of thermostable smallpox vaccine suitable for prolonged storage and use in tropical and subtropical regions of the world, and
   (*e*) study of the measures to be taken in order to avoid complications which might result from smallpox vaccination;

"2. RECOMMENDS to all governments:
   (*a*) that during 1959–1960 the population be vaccinated in countries in which principal endemic foci of smallpox exist; and
   (*b*) that during 1961–1962 additional vaccination of the population should be carried out in foci where the disease persists, and that subsequently revaccinations be given to the extent it becomes necessary in accordance with the experience acquired in each country;

"3. RECOMMENDS that all countries in which smallpox vaccination is compulsory continue to give smallpox vaccinations during the eradication of this disease throughout the world;

"4. CALLS upon medical scientists and scientific institutions active in the field of microbiology and epidemiology to stimulate their efforts towards improving the quality and the technology of the production of satisfactory smallpox vaccine resistant to the influence of temperature; and

"5. REQUESTS the Director-General to report to the Twelfth World Health Assembly on the progress made and the results obtained."

or the Health Assembly in the future" (World Health Organization, 1973a). The resolution included an important provision: "REQUESTS the Director-General to ensure, in accordance with the normal practice of the Organization, that any vaccine accepted for the anti-smallpox programme is of acceptable quality." Aware that standards for the potency and purity of vaccines of all types were not uniform throughout the world, and even nonexistent in some countries, Mr Milton P. Siegel, an Assistant Director-General of WHO, had drafted this cautionary proviso. As the Director-General noted: "... there were no international standards for vaccines. It was hoped that the Expert Committee on Biological Standardization would establish such standards soon" (World Health Organization, 1958b). This was done, in fact, in November 1958 and formalized in resolution EB23.R40 at the next session of the Executive Board (World Health Organization, 1959a). The stipulation with regard to vaccine quality was to prove most important, and after 1967 it was interpreted by WHO smallpox eradication staff as applying to all vaccines supplied to WHO-supported smallpox eradication programmes, whether or not they were provided through contributions to WHO (see Chapter 11).

The Director-General, as requested, submitted to the Executive Board in January 1959, and later to the Twelfth World Health Assembly, a lengthy report concerning the financial, administrative and technical implications of a smallpox eradication programme (World Health Organization, 1959b). It was based in part on replies to questionnaires received from 20 countries. The report noted that "it is generally agreed that eradication of smallpox from an endemic area can be accomplished by successfully vaccinating or revaccinating 80 per cent of the population within a period of four to five years". The global programme, as envisaged by WHO, would require national mass vaccination campaigns operated by a smallpox eradication service which would be "integrated with the general public health services" but "directed, or at least co-ordinated, centrally". Freeze-dried vaccine was recommended for use in tropical and remote rural areas and glycerolated vaccine where refrigerated storage and transport were available. The plan proposed that the Organization's Headquarters' budget should make provision for the recruitment of a full-time medical officer, epidemiological consultants (12 man-months per year) and laboratory consultants (6 man-months per year), as well as for the funding of an international conference and 2 training courses on vaccine production, and for the cost of distributing vaccine supplies. WHO regional office budgets would include provision for fellowships and consultants.

The Director-General's report estimated that approximately 977 million people then lived in endemic areas and, if all were to be vaccinated, the cost, calculated at US$0.10 per person, would amount to about US$97.7 million (World Health Organization, 1959b). No mention was made in the report of the

Table 9.1. Estimated cost of smallpox eradication as at 1959, and budget for smallpox programmes, 1958–1960 (US$)[a]

Region	Estimated cost of vaccination	WHO budget		
		1958	1959	1960
Africa	12 810 200	7 300	11 120	0
Americas	10 522 900	114 722[b]	97 370[b]	91 718[b]
South-East Asia	54 148 400	15 510	19 900[c]	14 286
Eastern Mediterranean	16 305 900	7 000	28 649	46 236
Western Pacific	3 955 500	0	0	0
Interregional		0	0	38 400
Total	97 742 900	144 532	157 039	190 640
Provided by WHO regular budget		74 197	55 568	111 081

Source: World Health Organization (1959b).

[a] The estimated costs of vaccination were calculated on the assumption that all persons in countries then infected would be vaccinated at a cost of US$0.10 each. The People's Republic of China, not then a Member State of WHO, was not mentioned in the report, nor were the costs for a programme there included in the estimates.

[b] Includes both WHO and PAHO funds, most of which were allocated to a yaws–smallpox eradication programme in Haiti.

[c] Includes US$16 000 from UNICEF.

Resolution WHA12.54, adopted at the Twelfth World Health Assembly in 1959

"Having considered the report of the Director-General on smallpox eradication [*Official Records of the World Health Organization*, **95**, Annex 18],

"Noting:

(1) that although great progress has been made in the eradication of the disease in some areas of the world, important endemic foci of smallpox still remain in other areas, especially in South-East Asia and Africa, from which the disease can be exported to countries already free of it;

(2) that eradication of smallpox from an endemic area can be accomplished by successfully vaccinating or revaccinating 80% of the population within a period of four to five years, as has been demonstrated in several countries;

(3) that sufficient scientific and technical information is available on the production of a suitable smallpox vaccine; and

(4) that although an eradication programme may require, for four or five years, an increase in the national efforts and financial obligations for the intensified campaign against smallpox, the heavy annual burden of continuing expenditure incurred for this purpose may be considerably lightened by increasing the interval between vaccinations once eradication may be considered to have been accomplished,

"1. EMPHASIZES the urgency of achieving world-wide eradication;

"2. RECOMMENDS to the health administrations of those countries where the disease is still present that they organize and conduct, as soon as possible, eradication programmes, making provision for the availability of a potent stable vaccine;

"3. REQUESTS the Director-General:

(1) to urge health administrations of those countries where the disease is still present to develop eradication programmes and to offer them any necessary technical guidance and advice;

(2) to provide for the necessary activities to further smallpox eradication programmes and for the assistance requested by national health administrations for this purpose, in his programme and budget for future years; and

(3) to collect from the countries concerned information on the organization and progress of their respective eradication programmes and to report further to the Thirteenth World Health Assembly."

People's Republic of China, which was not then a Member of WHO. The report pointed out that all countries were already spending considerable sums for the control of smallpox but speculated that the total costs, as estimated for each country, would be "appreciably higher than their present authorized budget provision for this purpose". The WHO budget for smallpox control was noted by the Director-General to have been negligible in previous years except in the Americas, where US$75 000 had been authorized in 1952 for this purpose, and US$144 089 in 1954. Although the report pointed out that "large sums are again set aside for the years 1958–1960 to continue the work" (Table 9.1), it also stated that even larger sums would be required in future years.

The report was discussed both at the Executive Board and subsequently at the Twelfth World Health Assembly (1959), although few substantive comments were made. At the conclusion of the debate, the delegates voted unanimously in favour of the programme. Nothing was said about the wide discrepancy between the identified need and the proposed WHO budget, nor was a request made for additional resources to be provided through voluntary contributions. Indeed, the only doubt about the feasibility of global eradication was expressed by a delegate from South Africa, who indicated that, without

knowing the exact position in all other countries, he could not say whether worldwide smallpox eradication was a practical proposition; nevertheless, he supported the resolution. Other delegates presented encouraging reports on their own successes in undertaking smallpox vaccination campaigns and in producing vaccine. The operative paragraphs of the resolution adopted (see box) were as significant for what was omitted as for what was said. No reference was made in them to the reporting of cases, the containment of outbreaks, or a timetable for the achievement of eradication, whether within a 10-year period, as suggested in the report presented by Professor Zhdanov, or in 5 years, as suggested in the resolution adopted by the Eleventh World Health Assembly.

Although the resources budgeted for the programme were modest indeed, Professor Zhdanov's ambitious proposal had been accepted, at least in principle, and the programme for the global eradication of smallpox formally began.

HISTORY OF THE CONCEPT OF ERADICATION

Introduction

The acceptance, as public health policy, of a planned programme designed to eradicate a disease over a large geographical area is a comparatively recent development, and the extension of such a policy to encompass the entire world is an even more recent one (Andrews & Langmuir, 1963). Even in 1958, and indeed for nearly two decades afterwards, the feasibility of global eradication of any disease was by no means universally accepted by the scientific community. However, smallpox was not the first disease to be considered seriously as a target for eradication, nor was the programme the first global campaign to be mounted. Because the personalities, attitudes and practices in previous programmes played an important role in the development and evolution of the smallpox eradication programme, it is important to consider briefly its historical antecedents.

Some would take issue with the assertion that smallpox was not the first disease to be considered for eradication, and in argument cite Jenner (1800) who wrote: "... Cow Pox, an antidote that is capable of extirpating from the earth a disease which is every hour devouring its victims: a disease that has been considered as the severest scourge of the human race!" Others at this time (Carl, 1802) echoed this belief, but the views were more expressions of hope than expectations for the implementation of a broadly conceived international programme.

Following Jenner's discovery, compulsory vaccination in several European countries resulted in the absence of the disease from a number of them over many years; also, in some small island states and isolated countries, smallpox occurred only sporadically, as a result of importations. However, government authorities, recognizing that smallpox could readily be reintroduced at any time, never spoke in terms of its eradication. The idea was not voiced again until 1949, at which time the Director of the Pan American Sanitary Bureau (the headquarters and secretariat of the Pan American Sanitary (later Health) Organization and WHO Regional Office for the Americas) proposed that such a programme should be undertaken throughout the Western Hemisphere. Meanwhile, efforts to control many other diseases, both animal and human, were being actively pursued.

The possibility of eradicating a disease or its vector emerged as a concept in the late 1800s with the improving scientific understanding of the causation and mechanism of transmission of various diseases and the discovery of methods for preventing them. As applied to a definitive policy, the term eradication appears to have first been used in 1884 in reference to a programme in the USA for the control of an animal disease, bovine contagious pleuropneumonia. Only 4 years later, however, Dr Charles Chapin (quoted in Soper, 1965) was to observe that preventive measures for any disease, if diligently applied, could potentially lead to eradication. He boldly asserted that any disease which could be prevented in part could be prevented in its entirety, and suggested that this might apply specifically to tuberculosis. Gradually, the term eradication came into wider use and, over the years, it was given a variety of definitions. Some authorities asserted that the term should be applied only when a disease pathogen had become extinct throughout the world, while others argued that it could mean simply the reduction in the incidence of a disease to the point where it ceased to be a public health problem (Cockburn, 1963).

In this publication, the term eradication is used in a narrower sense as suggested by its Latin derivation—*eradicare*, literally "to root

out" or "to tear out by the roots". Most eradication programmes, as such, have been concerned with communicable diseases, although diseases induced by toxic substances could certainly be eradicated by eliminating the offending substances. However, to use the term eradication with regard to programmes directed towards preventing traffic accidents or hunger, as some have done, is obviously inappropriate. For communicable disease programmes, Andrews & Langmuir (1963) provide the most widely accepted distinction between control and eradication: "Control is the purposeful reduction of specific disease prevalence to relatively low levels of occurrence, though transmission occurs frequently enough to prevent its permanent disappearance." Eradication, however, as they state, proceeds "to the point of continued absence of transmission within a specified area". While recognizing that the unqualified use of the word eradication signifies the world-wide extermination of a biological species, they accept the use of the word when applied to a specified geographical area—in effect, "area eradication".

The question of how large a specified area must be in order to apply usefully the term eradication has frequently been a contentious issue. Measles illustrates the quandary as to what the lower limits should be. The eradication of measles in a household or district in a city means little, since transmission periodically ceases in such small areas without the application of control measures, and reinfection regularly occurs. But should one speak of eradication of measles from a state or province, for example, or should the notion apply only to a continent or even larger area? Views differ on this question but most epidemiologists now prefer to use the term eradication only when the area covered is sufficiently large and geographically delimited and the characteristics of the disease or vector are such that reinfection or reinfestation is unlikely. Previous successful programmes, which are described below, are by these criteria properly called area eradication programmes.

Eradication of Animal Diseases

For a number of reasons, national programmes to eradicate animal diseases or pests antedate the first human disease eradication programmes and have been more consistently and vigorously pursued over the past century. To begin with, the measurable economic consequences of animal diseases have usually made it easier to obtain support for animal disease control programmes than for those for human diseases, whose economic consequences are often more difficult to quantify. Moreover, in dealing with animal diseases, useful strategies are available which cannot be employed in controlling human disease, the most important being the ability to apply rigid quarantine measures and to slaughter entire flocks or herds found to be infected. Finally, those concerned with animal husbandry have focused their attention more on the prevention of diseases than on their treatment.

It is not surprising, therefore, that the first planned programme whose stated objective was eradication was one intended to eliminate a disease of cows—bovine contagious pleuropneumonia (Hinman, 1966). This highly fatal disease had been brought from Europe to the USA (New York State) in 1843. Gradually, it spread to the large midwestern cattle-raising areas, and other countries eventually began to embargo imports of livestock from the USA. To deal with the problem, the United States Congress, in 1884, created the Bureau of Animal Industry, whose specific responsibility was to eradicate bovine pleuropneumonia. During a 5-year campaign the disease was eliminated, and the precedent and mechanisms for attacking other animal disease problems were established. Subsequent area-wide eradication programmes, again defined as such, were successfully conducted in the USA against a number of other animal diseases, including glanders (a disease of horses and mules), piroplasmosis (Texas fever) of cattle, and dourine (a sexually transmitted disease of horses) (Hagan, 1958). Rinderpest and sheep pox were eradicated from most countries in Europe late in the 19th century, and early in the present century eradication was accepted as the standard procedure for dealing with importations of serious exotic diseases of livestock into the industrialized countries of Europe, North America and Oceania.

The strategy differed from disease to disease, the approaches adopted depending on the mode of spread of the disease and the most effective point in the cycle of transmission at which to intervene in order to stop dissemination, whether by the isolation and slaughter of infected herds or the killing of vectors. Specific characteristics of the diseases in

question were vital to the success of these efforts, among the most important being that the diseases had been introduced comparatively recently into the target areas from other countries and that they tended to be geographically circumscribed. Moreover, it was usually possible to diagnose them easily, subclinical infections and carriers were rare, and none had become enzootic in wild animals. Success in solving the diverse problems involved suggested that there might be a number of microorganisms which clung so tenuously to an ecological niche that simple measures could be found to upset the balance of nature. Intensive, albeit costly, short-term programmes in these instances could be more productive and ultimately less expensive than long-term control efforts and the acceptance of continuing damage to livestock.

Thus, planned programmes for disease eradication on a national scale were a familiar concept to workers in veterinary medicine, but the achievements of such programmes were largely unknown to those concerned with human disease. For human diseases such as smallpox, cholera, plague and yellow fever, quarantine regulations were adopted to prevent their introduction into a country, and, in the case of smallpox, intensive vaccination campaigns were conducted when the disease was imported into smallpox-free areas. Until the present century, however, the term eradication, in the sense of a planned programme whose stated aim was the elimination of a human disease throughout a defined geographical area, was not used.

The First Eradication Programmes for Human Diseases—Hookworm and Yellow Fever

Hookworm was the first disease to be considered seriously as a candidate for global eradication, and the first for which a programme was actually mounted. That programme, begun in 1909, was soon followed by a global programme for the eradication of yellow fever. Since the operational methods and styles of leadership adopted in subsequent eradication programmes had their roots in these two campaigns, their history is of interest.

From what is now known of the biology of the two diseases, neither was a reasonable candidate for eradication, but, when the programmes began, inadequate scientific knowledge, coupled with a visionary outlook and excessive optimism, made them appear suitable. The extensive campaigns which ensued left an important legacy in the development of public health services and education in many countries. But, as the programmes progressed and more was learned about these and other diseases, it became increasingly apparent that the causative organisms were remarkably well adapted to their ecological niches and had more intricate and complex relationships with the human and natural environments than had been appreciated. Gradually, it became apparent that disease eradication was a formidable, perhaps even an unattainable, goal (Smith, 1934; Burnet, 1940; Dubos, 1959, 1965).

Hookworm eradication

Early this century, a United States public health official, Dr Charles Wardell Stiles, had the vision of totally interrupting the spread of hookworm in the southern states of his country by a systematic campaign in which infected persons would be identified by stool examination and their infections eliminated by drug therapy. The construction of sanitary privies during this period would prevent faecal contamination of the soil and thus break the transmission cycle, in which hookworm larvae enter the human body through the skin of the feet, migrate to the intestinal mucosa where they feed on blood in the capillaries, and shed eggs that are passed in the faeces to the soil and there develop into larvae. Advisers to Mr John D. Rockefeller, then increasing his support to philanthropic projects, studied the proposition and pronounced it sound. The Rockefeller Sanitary Commission for the Eradication of Hookworm in the United States was established in 1909, and a sum of US$1 million was pledged to be spent over 5 years. Dr Wickliffe Rose, a professor of philosophy, was appointed director of the programme.

Over the first 5 years of the hookworm eradication programme in the USA, extensive operations were carried out in 11 states. By 1914, the Commission reported having screened more than 2 million persons, of whom 500 000 were treated in mobile dispensaries; more than 250 000 rural homes were inspected by sanitary personnel. This undertaking, involving thousands of workers, was the largest and most complex community-

wide health programme ever to be carried out in the USA up to that time.

With the establishment in 1913 of the Rockefeller Foundation, Dr Rose was made Director of its International Health Commission, into which the Sanitary Commission was incorporated. The Foundation made a policy decision to "confine itself to projects of an important character, too large to be undertaken, or otherwise unlikely to be undertaken, by other agencies" and to "go to the root of individual or social ill-being and misery" (Fosdick, 1952). Hookworm eradication clearly satisfied these criteria. Thus, as its first initiative, the Foundation's trustees decided "to extend to other countries and people the work of eradicating hookworm disease as opportunity offers, and so far as practicable to follow up the treatment and cure of the disease with the establishment of public sanitation and the spread of scientific medicine". In the following years, cooperative programmes were extended to 52 countries on 6 continents and to 29 island groups.

Not for a number of years were careful field studies conducted to determine whether, given effective execution of the prescribed strategy and tactics, the parasite had actually been eradicated. When such studies were finally conducted, they showed that, even with an effective programme, infection rates did not significantly diminish, although those infected had fewer worms and therefore less illness due to the disease (Smillie, 1922). It was apparent that the biology of hookworm was far more complex than had been appreciated, and that the methods of attacking it were inadequate. Dr William Cort, then the leading authority on hookworm disease, pleaded for more research in both areas but, in doing so, studiously avoided using the word "eradication" (Cort, 1921); the Foundation, at least so far as hookworm was concerned, eventually followed suit. The control programme was remarkably successful in establishing a network of 4-person county health departments (health officer, sanitary engineer, public health nurse and secretary) in the southern USA, and many other countries created similar structures, but hookworm has remained a problem in most developing countries.

Yellow fever eradication

Success in the control of yellow fever in Cuba and Panama laid the groundwork for yet another, apparently more plausible, programme for disease eradication for which the Rockefeller Foundation was also to provide leadership and substantial support. Recurrent severe epidemics of yellow fever had plagued cities in the USA since the 17th century, but the disease had never become endemic. By the end of the 19th century, it was believed that most of these epidemics were the consequence of importations of the disease from Cuba (Strode, 1951). Thus, when Cuba was occupied by United States forces in 1898, during the Spanish-American War, yellow fever control was of special interest to the authorities.

In 1900, a government Yellow Fever Commission, directed by Major Walter Reed, was charged with the responsibility for ascertaining the cause and mode of spread of the disease and for finding methods for its control. A series of brilliant studies rapidly provided the critical insights into the epidemiological behaviour of the disease that permitted an effective control programme to be implemented. Building on the belief of the Cuban scientist, Dr Carlos Finlay, that a mosquito vector was involved, the Commission demonstrated conclusively that the vector was the mosquito *Stegomyia fasciata* (*Aedes aegypti*), which bred almost exclusively in and around houses. Moreover, drawing on observations by Dr Henry Carter, the Commission showed that there was an interval of 9–16 days between the time at which a mosquito took a blood-meal and the time at which it could transmit infection, and that person-to-person spread via excreta or fomites never occurred (Reed et al., 1900). If mosquito control measures were to be introduced and patients isolated in screened quarters, the prospects for yellow fever control looked hopeful.

The Chief Sanitary Officer for Cuba, Dr William Gorgas, then a major in the United States Army Medical Corps, assumed responsibility for the programme. Patients were isolated in screened quarters, and breeding sites for the mosquitos were eliminated by the removal of discarded cans and bottles, in which they bred; in addition, cisterns were covered with netting and kerosene was applied to water surfaces which could not be otherwise treated (Gorgas, 1911b). The programme was a quasi-military operation, which began on 4 February 1901 and in which teams of 3 inspectors were assigned responsibility for groups of 1000 houses, to be inspected at the rate of 30 houses per day. On

28 September 1901, the last case of yellow fever occurred in the city of Havana proper, only 8 months after the programme had begun—indeed, some 2 weeks before Reed & Carroll (1902) discovered that the disease was caused by a filterable virus. Shortly thereafter, the disease was discovered in a suburb of Havana, but similar operations there promptly terminated transmission and yellow fever vanished from Cuba. Dr Gorgas, in his report of 12 July 1902 to Brigadier General Leonard Wood (Gorgas, 1911a), stated: "I look forward in the future to a time when yellow fever will have entirely disappeared as a disease to which man is subject, for I believe that when the yellow fever parasite has become extinct it can no more return than the dodo or any other species of animal that has disappeared from the earth."

The efficacy of the measures taken was soon confirmed in Panama. In June 1904, Dr Gorgas was named Chief Sanitary Officer for the Isthmus of Panama, where the Panama Canal was then under construction. After an epic 16-month effort, Panama also became free of yellow fever (McCullough, 1977). Success was achieved even though the campaigns were restricted to urban areas, and the vector was substantially reduced in numbers but not eliminated. In 1908, Dr Oswaldo Cruz added independent confirmation of the efficacy of Dr Gorgas's methods by eliminating yellow fever from Rio de Janeiro. On the basis of these experiences, Dr Gorgas concluded that the transmission of yellow fever could be sustained only in the more densely populated urban areas and that eradication could be achieved by short-term campaigns against *A. aegypti* in a few key endemic urban centres (Gorgas, 1908).

Some 6 years later, in 1914, the desirability of testing this hypothesis on a wider scale was suggested to Dr Rose during a visit to Asia. Throughout Asia, he found health officials to be profoundly concerned that yellow fever might be imported as a consequence of the opening of the Panama Canal in that year and the resulting increase in maritime traffic. Although yellow fever did not then occur in Asia (nor is it known to have occurred since that time), the potential mosquito vectors were widely prevalent. If the disease were introduced, massive epidemics could be expected. Dr Rose consulted Dr Gorgas, then Surgeon-General of the United States Army, who expressed the opinion that yellow fever could be "eradicated from the face of the earth within a reasonable time and at a reasonable cost" (Fosdick, 1952). On 26 May 1915, definitive action was taken by the International Health Commission to set such a programme in motion, by its adoption of the following resolution:

"Whereas, yellow fever has been endemic in tropical and subtropical America for centuries, constituting a serious menace in the infected areas and a perennial source from which epidemics have spread to more remote regions both in America and Europe, involving great loss of life and interrupting industry and trade over vast areas, and

"Whereas it has been shown by the work done in Havana and Panama under the direction of Dr William C. Gorgas and in Rio de Janeiro under the direction of Dr Oswaldo Cruz that the infection can be eradicated even in communities where it is endemic, and

"Whereas, the opening of the Panama Canal and the changing of trade relations resulting therefrom have given rise to widespread apprehension that yellow fever may be introduced into the Orient; and that once endemic in these densely populated regions it would become a permanent menace to the rest of the world; therefore

"Be it resolved, that the International Health Commission is prepared to give aid in the eradication of this disease in those areas where the

JOHNS HOPKINS UNIVERSITY, 1916

Plate 9.2. William Crawford Gorgas (1854–1920), after successfully freeing Cuba and Panama of yellow fever, encouraged the Rockefeller Foundation to support a global effort to eradicate the disease. Launched in 1918, with Gorgas as director, this work was the first serious attempt to eradicate a human disease. Its principal technology, vector control, became the basis of subsequent efforts to eradicate the mosquito vectors of malaria and other diseases.

infection is endemic and where conditions would seem to invite cooperation for its control." (Strode, 1951.)

It was anticipated that eradication in the Americas would require perhaps 5 years; further study would be needed to determine a timetable for Africa, the only other endemic area. Soon afterwards, a resolution calling for the eradication of yellow fever from the Americas was approved by the II Pan American Scientific Congress (1915–1916) (Duffy, 1977). Between 1916 and 1949, the Rockefeller Foundation was to spend US$13.8 million on yellow fever control (Strode, 1951).

With the new yellow fever eradication programme and a continuing campaign against hookworm, a critical need arose for skilled physicians trained in organization and management and having a scientific understanding of these diseases. Partly to meet this need, Dr Rose proposed in 1916 that schools of public health should be founded with support from the Rockefeller Foundation. The first of these was established at The Johns Hopkins University. Over the succeeding decade, 23 other schools based on this model were established and supported in 20 different countries in North and South America, Europe and Asia.

The start of the yellow fever eradication campaign was delayed by the First World War, but in 1918 programmes supported by the Rockefeller Foundation were launched in Guayaquil, Ecuador, and in towns on the Pacific coast of South America at risk of infection from Guayaquil. They were soon extended to other known or suspected foci in the Central American countries, Mexico and Peru. The campaign was predicated on the belief that there was no animal reservoir and that yellow fever was unable to persist as an endemic disease in urban populations of less than 50 000. Campaigns to interrupt transmission were thus conducted only in the cities and larger towns but were extended to smaller towns to control outbreaks when they occurred. Transmission appeared to cease when breeding sites of *A. aegypti* were found in only 5% or fewer of the houses, and thus control, not eradication, of the vector constituted the basic strategy. At first it was dramatically successful. Transmission ceased in Guayaquil after only 6 months, in Peru in 1921 and in Central America in 1924.

Brazil organized its own programme in 1919 but halted it in 1922 when the "disease had disappeared from the statistics" (Soper, 1965). Yellow fever reappeared in 1923, however, and the Rockefeller Foundation was requested to provide support. Again, rapid progress was made, and from April 1927 to March 1928 no cases were reported from anywhere in the Americas. Meanwhile, in preparation for programmes in Africa, the Rockefeller Foundation established laboratories there to undertake special studies of the disease.

In March 1928, however, cases of yellow fever were again detected in north-east Brazil and, in May, cases appeared in the capital, Rio de Janeiro—the first cases there since Dr Cruz's campaign 20 years before. From Rio, cases spread rapidly and widely throughout the country, the first such spread of yellow fever from a key urban centre since the programme had begun. At the same time, outbreaks whose sources could not be identified occurred also in Colombia and Venezuela. Many people began to express doubts about the feasibility of yellow fever eradication, and the Rockefeller Foundation, simultaneously faced with a failing anti-hookworm campaign, began to be criticized for its support of disease eradication (Soper, 1965).

The crisis of the Rio de Janeiro epidemic precipitated a series of changes which, in turn, altered the administrative structure of the programme and eventually led to a redirection of its goals. At the same time, it established precedents for centralized, independent programme operations which were to characterize subsequent malaria eradication programmes. Field activities, previously directed by a combination of national and state authorities and Foundation staff, were integrated over a 3-year period into a single National Yellow Fever Service under the direction of Dr F. L. Soper, a Foundation staff member who had worked in the anti-hookworm campaign in Brazil since 1920. No national disease control programme of such magnitude had been undertaken before this time. It was supported in part by the Brazilian government and in part by the Foundation.

The 1928–1929 outbreaks, some of which occurred outside urban areas, dramatized the need for disease surveillance. Information as to where yellow fever was occurring was vital but until 1930, there was no organized system for detecting and reporting cases. Because programme staff had assumed that endemic disease could persist only in urban areas with populations of 50 000 or more, and because

the disease was severe and often fatal, they believed that the presence of yellow fever would inevitably become known without much delay. In fact, few hospitals or health units outside urban areas regularly reported suspected cases, and from most areas there were no reports at all. Not until 1930 was it appreciated that the absence of reports did not necessarily mean the absence of cases. To obtain accurate reports, however, was difficult because, clinically, yellow fever resembled other illnesses with fever and jaundice. Neither virology nor immunology was then sufficiently advanced for satisfactory diagnostic methods to have been developed, but, fortunately, the liver pathology of patients with yellow fever was characteristic of the disease. Thus, pathological diagnosis was employed to determine the etiology in fatal cases. To obtain the necessary specimens, the Brazilian government ordered that a specimen of liver should be obtained from all patients who had died within 11 days of the onset of a febrile illness (Soper et al., 1934). A viscerotome was devised (Rickard, 1931) that was simple enough to be used by a layman after brief training. A field organization of viscerotomists was set up, a small payment being made for each specimen provided. It soon became apparent that there was widespread endemic disease in rural areas of the north-east (Soper et al., 1933), and in 1932 the first definitive evidence was obtained that wild animals constituted a jungle reservoir of the disease (Soper, 1936), a fact soon confirmed in other countries.

Aedes aegypti Eradication

With the discovery of the existence of a virus reservoir in wild animals, the eradication of yellow fever was no longer realistic. However, in the course of reorganizing the yellow fever programme, Dr Soper had established a rigidly disciplined and meticulously organized vector control programme in coastal cities throughout north-east Brazil. It soon became apparent that in urban areas, the peri-domestic *A. aegypti* mosquito could be entirely eliminated through the removal or destruction of breeding sites around human habitations. Reintroduction occurred, however, unless suburban areas were similarly controlled, and this implied that eventually programmes would be required in the interior of the country as well. A programme for the eradication of a mosquito species was an entirely different proposition from one designed only to reduce it to low levels. It required a far more intensive and disciplined effort over a far wider area and for a much longer time than that needed for the Gorgas-type yellow fever eradication programme in Havana. However, in view of the already considerable investments of the Brazilian government and of the Rockefeller Foundation and the existence of a highly disciplined organization in the field, Dr Soper in 1934 proposed a new objective—the eradication of *A. aegypti*, the urban vector of the disease. This was the strategy that he subsequently pursued, although it did not become the declared policy of the Brazilian National Yellow Fever Service until 1942.

With the eradication of yellow fever no longer feasible and that of *A. aegypti* a more costly and less certain proposition, the Rockefeller Foundation decided to withdraw its support but, because of Dr Soper's position, this was diplomatically difficult. Dr William Sawyer, of the Foundation, wrote to him on 24 September 1935 stating: "The yellow fever service has grown to such a size that you have practically become a Government official in charge of a large division of the Health Department ... it is hardly consistent with our general policies" (Duffy, 1977). The decision to withdraw support was postponed on several occasions at the request of the Brazilian government, but finally, at the end of 1939, support ceased and responsibility for the programme in Brazil was transferred from the Foundation to the government. Dr Soper, however, remained on the staff of the Foundation.

Eradication of Another Mosquito Vector—*Anopheles gambiae*

Because of the failure to eradicate yellow fever, the concept of eradication might well have been more thoroughly discredited had it not been for the unexpected discovery and the subsequent elimination of a focus of the mosquito *Anopheles gambiae*, near Natal in north-east Brazil (Duffy, 1977). This African mosquito, an exceptionally efficient vector of malaria, was apparently imported into Brazil in about 1930, soon after the establishment of a rapid mail service between Dakar (Senegal) and Natal (Soper & Wilson, 1943). Epidemic malaria occurred that year within an area of a

few square kilometres in which the mosquito was first found. Although the vector was quickly eliminated from Natal, it spread inland, and in 1938 severe epidemics began to occur over large areas of 2 states. In all, 31 000 square kilometres were found to be affected (Fosdick, 1952). Dr Soper proposed that an *A. gambiae* eradication programme should be started immediately. He rightly portrayed—in the most dire terms—the implications of a continent-wide spread of the mosquito, but support was not immediately forthcoming from either the Rockefeller Foundation or the Brazilian government. To some, it was seen as little more than an excuse to prolong the life and extend the scope of the vector control services. However, in January 1939, with reluctant financial support from the Foundation as well as substantial government funds, an anti-malaria service was established by presidential decree, its direction being entrusted to the Foundation and to Dr Soper.

The problem was a major one, more than 100 000 cases of malaria being detected in May 1939 alone, but the strategy required was entirely different from that used to eliminate *Aedes aegypti*. *Anopheles gambiae* bred widely in shallow pools of residual rain-water which were exposed to the sun and without vegetation. It did not usually lay eggs in deep or running water or water which was salty or shaded. During the 4-month rainy season in the area concerned, breeding took place in any small depression in the ground, such as wheel tracks and hoofprints, which could retain water for 8–9 days. With the advent of the dry season, however, the tropical sun and low humidity restricted breeding essentially to isolated pools in the beds of large rivers.

The approach which was adopted required a staff of about 4000. The boundaries of the infested area were determined and posts established at which all vehicles and boats leaving the area were fumigated. In the infested areas, vector control staff carried out regular inspections, applying Paris green to all possible breeding sites and spraying houses with pyrethrum (Duffy, 1977). They were able to do little more than control breeding during the rainy season, but when the dry season came and breeding sites were few, large areas could rapidly be cleared of the vector. A rigorously disciplined and closely supervised vector control staff, organized with the meticulous attention to detail which had characterized the *Aedes aegypti* programme, succeeded in these efforts, the last focus of *Anopheles gambiae* being discovered in November 1940, less than 2 years after the campaign had begun.

Although *A. gambiae* was a recently introduced vector and less well established in Brazil than in its native African habitat, its eradication from Brazil was nevertheless a dramatic achievement which, at the outset of the programme, had been considered by most to be hopelessly unrealistic. From the experience of this campaign, as well as those against *A. aegypti* and the Mediterranean fruit fly in Florida (USA), Dr Soper concluded that "selective species eradication", not only of *A. gambiae* but of other vectors as well, was in many instances a sound and ultimately less expensive approach than the control of the vector and of the disease (Soper & Wilson, 1943). The belief was reinforced when, in July 1944, he assumed direction of an *A. gambiae* eradication programme in Egypt, into which the vector had apparently been introduced in about 1942, causing major epidemics of ma-

WHO / T. FARKAS, c. 1966

Plate 9.3. Fred Lowe Soper (1893–1977) was the most ardent proponent of the policy of disease eradication. While on the staff of the Rockefeller Foundation, he directed the yellow fever eradication programme in Brazil in the 1930s, a programme he transformed into one designed to eradicate the principal mosquito vector (*Aedes aegypti*). Subsequently, he directed programmes to eradicate infestations of *Anopheles gambiae* in Brazil and Egypt. As the Director of the Pan American Sanitary Bureau, 1947–1959, he was instrumental in persuading the Pan American Sanitary Organization to embark on regional programmes for the eradication of *A. aegypti*, smallpox, yaws and malaria.

laria. An estimated 120 000 deaths had already occurred when the Egyptian government requested the help of the Rockefeller Foundation and Dr Soper (Duffy, 1977). Employing the same manual and methods as had been used in Brazil, an effective campaign quickly took shape and, in February 1945, the last focus was eliminated.

As Dr Soper saw it, success lay in "vigorous and effective action rather than refined measurement of the problem" (Duffy, 1977). He had no malariologists on his staff and saw no need for them. He quoted Dr Ronald Ross (Ross, 1911) on the need for "learning by doing":

"Amateurs are fond of advising that all practical measures should be postponed pending carrying out detailed researches ... In my opinion this is a fundamental mistake ... In practical life we observe that the best practical discoveries are obtained during the execution of practical work and that long academical discussions are apt to lead to nothing but academical profit." (Soper & Wilson, 1943.)

Dr Soper's advocacy of, and belief in, the principle of eradication was a major factor in later decisions to undertake other eradication programmes. The major constraints, he believed, lay primarily in the lack of vision of health administrators rather than in the lack of appropriate technology. With a meticulously executed field programme directed by dedicated and imaginative staff, the inconceivable became possible.

As early as 1934, Dr Soper had been convinced of the feasibility of eradicating *A. aegypti* from the Western Hemisphere. His opportunity to pursue the matter came in 1947 when he was elected Director of the Pan American Sanitary Bureau (PASB). He was a forceful and imaginative administrator, who extended and reoriented PASB's activities, converting it from a body which dealt principally with matters of international quarantine and was staffed entirely by officers seconded from the United States Public Health Service, into the secretariat of a fully fledged international organization, the Pan American Sanitary (later Health) Organization (PASO, later PAHO). One of the first acts of the Directing Council of PASO, in September 1947, was to adopt a resolution:

"1. To entrust to the Pan American Sanitary Bureau the solution of the continental problem of urban yellow fever, based fundamentally on the eradication of *Aedes aegypti* ...

"2. To develop the program under the auspices of the Pan American Sanitary Bureau, which ... shall take the necessary measures to solve such problems as may emerge ... whether they be sanitary, economic or legal." (Pan American Health Organization, 1971a).

As Dr Soper noted, "For the first time the governments of an entire region committed themselves to the continental solution of a common health problem" (Soper, 1965). Ironically, the goal was never achieved. At one time or another *A. aegypti* eradication was certified in all the countries of the Americas except Colombia, the USA, Venezuela and some of the Caribbean islands. However, reinfestations repeatedly occurred and a US$54 million programme in the USA, which was not begun until 1964, was terminated in 1968, its failure resulting to a large extent from the fact that there were substantially more breeding sites than had been anticipated and that vector control staff could not legally be given the unrestricted right of entry to all premises to look for them (Fontaine et al., 1965).

Programmes for the Eradication of Malaria, Yaws and Other Human Diseases

Dr Soper's advocacy served to encourage acceptance of the principle of eradication as the defined objective of disease control programmes. Resolutions were adopted uncritically supporting the eradication of other diseases, only limited consideration being given to the technical feasibility, the available resources or the strategy to be used. The XIII Pan American Sanitary Conference (1950) committed PASB to regional programmes for the eradication of yaws, malaria and smallpox. Later, the World Health Assembly committed WHO to global eradication programmes for malaria (1955) and smallpox (1959). Events leading to the decision to undertake the eradication of smallpox are described in a subsequent section, but a brief description of the other initiatives and their outcomes is pertinent.

The malaria programme

Of all the eradication programmes, that for malaria represented by far the largest commitment, in terms both of the number of countries involved and of the resources de-

ployed. It was, moreover, the only global disease eradication programme other than that for smallpox to be approved by the World Health Assembly. Because malaria eradication activities antedated those of the smallpox eradication programme and continued through much of its course, they are of special interest. The successes and failures of its policies provided guidance in formulating smallpox eradication strategy, and its continuing operations competed both for resources and for the attention of national and international authorities until the mid-1970s.

Malaria was and is one of the most serious of the health problems of tropical and subtropical countries throughout the world. Until the Second World War, the principal control methods available were costly ones—drug therapy for the disease and mosquito control through environmental management and the application of chemicals to destroy larvae and adult mosquitos. Where these measures were diligently applied, especially in areas in which mosquitos did not breed throughout the year, reasonable control could be achieved; such cases as did occur could be treated, usually successfully, with drugs. In few of the non-industrialized countries, however, was it possible to achieve such control measures outside urban centres.

However difficult the control of malaria, the idea that eradication was possible was raised as early as 1916 (Hoffman, 1916) and actually adopted, in part, in a resolution of the II Pan American Scientific Congress in January of that year, which urged "... that all American countries inaugurate a well-considered plan of malaria eradication and control" (Jeffery, 1976). Little was achieved, but in the early 1940s the discovery of the insecticide DDT radically changed the situation. DDT, it was found, had a remarkable property in that it retained its toxicity for mosquitos over many months when applied to surfaces (Soper et al., 1947). Most malaria-bearing anophelines, after taking a blood-meal, rested on a nearby surface. If this was a wall coated with DDT, they died before they could transmit the disease.

As increasing quantities of inexpensive DDT became available, it was used in many malaria control programmes in different parts of the world. The effect on malaria morbidity and mortality was dramatic. In Venezuela, for example, in states with an accurate death registration system, mortality rates plummeted from a median of 173 per 100 000 population in 1941–1945 to 2 per 100 000 in 1949 (Gabaldón, 1951). Similar results were observed in countries as distant and disparate in character as Ceylon (Sri Lanka) and China (Province of Taiwan). The complete disappearance of malaria from infected areas in Greece and Italy, as well as from the whole of Sardinia, was even more dramatic (Logan, 1953). Of particular interest was the discovery in Greece that even when DDT spraying was temporarily stopped owing to a shortage of the insecticide, the disease did not return (Pampana, 1963). A DDT-based malaria eradication programme throughout infected areas of the USA (Andrews, 1951) also appeared to have stopped transmission towards the end of the 1940s, although surveillance data collected at a later stage revealed that the campaign had actually begun some time after transmission had effectively been stopped by traditional measures (Langmuir, 1963).

These successes, real or imagined, spurred the imagination of the eradicationists. Thus, in 1948, Dr E. J. Pampana proposed that global malaria eradication should be undertaken (Pampana, 1948). This proposal was translated into policy 2 years later, in 1950, when the XIII Pan American Sanitary Conference, encouraged by Dr Soper, recommended that PASB should "collaborate with

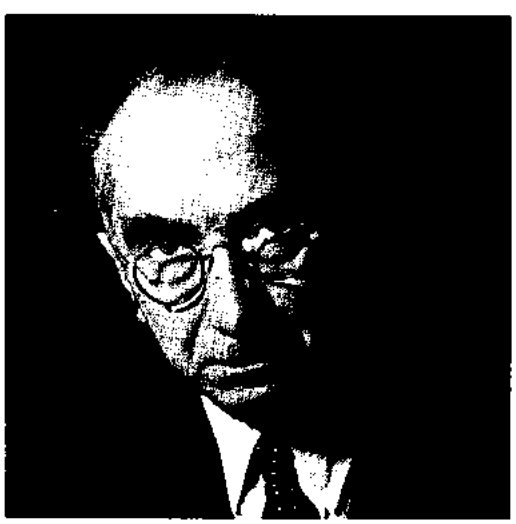

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Plate 9.4. Emilio J. Pampana (1895–1973), a distinguished Italian malariologist, in 1948 proposed the global eradication of malaria, a commitment adopted by the World Health Assembly in 1955. He was on the WHO staff from 1947 to 1958, first as chief of the malaria section, later as the first Director of the Division of Malaria Eradication.

the malarious nations of the Americas in national malaria eradication programmes" (Pan American Health Organization, 1971a). Little note was taken of the fact that malaria transmission had so far been interrupted only in the more developed areas of the world or where the mosquito vector was able to breed for only part of the year.

The financial and personnel resources of PASB were limited, and, as Dr Soper was to observe: "The action of the conference on malaria eradication proved to be ahead of its time; the PASB itself was not sufficiently developed to give adequate leadership" (Soper, 1965). During the succeeding 4 years, the successful use of DDT was reported from other countries but further progress in malaria eradication in the Americas was limited. Although United States bilateral assistance for malaria control in the Americas amounted to US$60 million between 1942 and 1957 (International Cooperation Administration, Expert Panel on Malaria, 1961), this was far too little to tackle the problem seriously.

Greater international support was required. The key to obtaining that support was provided by the first scattered reports, in 1951, of mosquito resistance to DDT—the insecticide on which the whole programme of malaria control depended (Pampana, 1963)—thus raising the spectre of widespread vector resistance that would render DDT useless as a means of control. It was argued that, in view of this situation, the only workable strategy was to carry out an intensive global programme to eradicate malaria before the problem of resistance became widespread. When confronted with this scenario, the XIV Pan American Sanitary Conference, in October 1954, declared regional malaria eradication to be an emergency need and authorized a special fund of US$100 000 for administrative expenses (Pan American Health Organization, 1971a). Immediately thereafter, UNICEF also agreed to provide support (Soper, 1960).

By no means were all scientists convinced that eradication was a feasible objective, given the tools available (Farid, 1980; Downs, 1981). For Dr Soper, however, the answer, as with his *Aedes aegypti* and *Anopheles gambiae* campaigns, lay in an aggressive approach, in meticulous organization, and in tackling the problems as they emerged. As he was to point out later, the eradication programme for *A. aegypti* had required no new technical or administrative methods—merely the careful supervision and checking of work and the standardization of operating procedures. He believed that there was an "essential identity of the malaria program with that of yellow fever" (Soper, 1960). To subscribe to the objective of malaria eradication required an act of faith. To those who doubted, Dr Soper quoted the pessimistic 1945 Presidential Address of the sceptical Dr Henry Johnson, President of the National Malaria Society in the USA: "I feel this [malaria eradication in the USA] is an untenable concept as we do not yet know in sufficient detail just where and under what conditions the disease occurs" (Johnson, 1946). It became apparent only a few years later that malaria eradication in the USA was imminent, if not already achieved, even as Dr Johnson spoke.

In May 1955, less than a year after the Pan American Sanitary Conference decided on an emergency programme for the eradication of malaria from the Americas, the Eighth World Health Assembly endorsed this as a worldwide policy, and WHO was committed to its first global eradication programme. In the words of resolution WHA8.30, the Health Assembly:

> "Considering that the ultimate goal of malaria-control programmes should be the eradication of the disease,
>
> 1.1. REQUESTS governments to intensify plans of nation-wide malaria control so that malaria eradication may be achieved and the regular insecticide-spraying campaigns safely terminated before the potential danger of a development of resistance to insecticides in anopheline vector species materializes." (World Health Organization, 1973a.)

A Malaria Eradication Special Account for voluntary contributions was created and programmes began throughout much of the world, although not in sub-Saharan Africa.

The WHO Expert Committee on Malaria, which met a year later, was extremely cautious, however, when it discussed the feasibility of malaria eradication. In its report, it noted only that eradication "has been accomplished and has shown that it can withstand the test of time in a number of areas in the Mediterranean countries and the Americas" and that "malaria eradication might have still remained an exceptional aim if events had not made it a preferable one to mere control" (WHO Expert Committee on Malaria, 1957). Nothing was said, or could be said, about the prospects for eradication in sub-Saharan Africa in particular. No successful national programmes had been carried out there, most

Unacceptable Doubts about Malaria Eradication—Reflections of Dr Wilbur Downs

"In the early 1950s, when malaria eradication became the cause, Dr. Soper came to Mexico to persuade Mexico to get aboard the band wagon. Since I was in Mexico and had been there for 6 years, I was summoned to be with Soper in the office of the Ministry of Health, where multimillion dollar issues were being discussed. My own program budget at the time was less then $50,000 per annum. As I sat in the Minister's office, I heard some amazing things being said, things quite opposite to my own experience, and spoke up saying that there was evidence to indicate very serious problems in the way of eradication in Mexico. Some problems related to the unreconstructed habits of the principal vectors, *Anopheles pseudopunctipennis* and *Anopheles albimanus*. Some problems related to the absorption and accelerated decomposition of DDT by the clays found in the mud of adobe walls. Soper strode over to me, put both hands around my neck and shook me vigorously, saying at the same time that it was this kind of talk which was impeding the malaria eradication effort around the world. Not long after that episode, I was advised by my organizational superiors that my malaria study project in Mexico was superfluous, and would be terminated." (Downs, 1981.)

of the countries concerned were at an early stage of development and there was year-round breeding of the vectors in many areas. Given these and other problems, there was good reason to believe that eradication could not be achieved (Macdonald, 1957). Little mention was made by WHO thereafter of the fact that "Africa south of the Sahara was at present excluded from the eradication programme, for physical, economic and developmental reasons complicated by high endemicity and prolonged transmission factors" (World Health Organization, 1957).

The visionary goal of the global eradication of a disease as serious as malaria was enthusiastically welcomed by politicians and agencies around the world, as well as by those concerned with public health. The programme was foreseen to be a costly one but it was supported by multilateral and bilateral agencies as no previous international health undertaking had ever been. At the same time, participation by countries in a fully fledged eradication effort was encouraged by the policy of providing funds only to countries which agreed to accept the objective and strategies of eradication. By 1958, 63 countries had either started malaria eradication programmes or had converted their control programmes to eradication campaigns; 700 million people, 65% of the population in malarious areas, lived in these countries (Yekutiel, 1981).

Increased expenditures from the WHO regular budget were substantially augmented by voluntary contributions to the WHO Malaria Eradication Special Account, and supported by other funds administered by WHO, including those provided by UNICEF and the United Nations Expanded Programme of Technical Assistance (later named the United Nations Development Programme) (Table 9.2). The malaria eradication programme quickly became WHO's most important activity and in 1962, when contributions to the Special Account diminished, funds from WHO's regular budget, although originally intended for other purposes, were transferred to the Special Account. Expenditures from funds administered by WHO increased from US$2.4 million in 1955 to US$13.7 million in 1958; the number of staff posts likewise increased, from 84 in 1955 to 259 in 1958 and to 577 in 1960. From 1955 to 1958, the malaria eradication programme accounted for 3.6% of WHO's regular budget and 34.8% of all funds and its disposal (Table 9.3). Between 1959 and 1966, obligations for malaria eradication increased substantially, accounting for 10.8% of WHO's regular budget and 27.2% of all funds placed at the Organization's disposal. In comparison, smallpox control received little support and, after the global eradication programme began in 1959, expenditure remained below 1.0% until 1967. Bilateral contributions to national programmes were also greatly augmented and national government budgets were vastly increased. An estimated US$1400 million were expended from all sources for malaria

Table 9.2. Number of WHO staff posts and estimated expenditure for malaria eradication from the WHO regular budget and from funds provided to WHO through the Malaria Eradication Special Account and by other international agencies, 1955–1970[a]

Year	Expenditure (US$)				Number of WHO staff posts
	Total	From WHO regular budget	From WHO Malaria Eradication Special Account	From other sources[b]	
1955	2 402 480	118 634	–	2 283 846	84
1956	3 870 160	420 040	–	3 450 120	144
1957	9 673 473	533 047	28 247	9 112 179	181
1958	13 663 753	528 109	3 027 213	10 108 431	259
1959	13 352 868	533 106	3 749 390	9 070 372	498
1960	13 729 432	511 051	3 894 972	9 323 409	577
1961	14 553 023	249 860	3 777 891	10 525 272	565
1962	13 902 844	2 408 723[c]	2 538 656	8 955 465	544
1963	13 247 377	4 403 856[c]	814 657	8 028 864	625
1964	13 268 814	5 699 052[c]	(159 584)[c]	7 729 346	607
1965	12 651 876	4 701 142	903 543	7 047 191	604
1966	13 191 119	5 206 999	984 252	6 999 868	532
1967	14 195 016	6 217 708	893 515	7 083 793	534
1968	14 349 674	6 660 853	1 009 191	6 679 630	501
1969	13 681 987	6 871 085	310 704	6 500 198	495
1970	10 848 638	5 426 671	–	5 421 967	355

[a] Estimates derived from WHO financial reports, WHO proposed programme and budget volumes and reports to the Directing Council of PAHO.

[b] United Nations Expanded Programme of Technical Assistance, UNICEF, PAHO regular budget and PAHO special malaria fund.

[c] In 1962, 1963 and 1964, WHO regular budget funds were transferred to the Malaria Eradication Special Account in amounts, respectively, of US$2 million, US$4 million and US$5 363 000 (World Health Organization, 1963a, 1964a, 1965a). These expenditures are shown in the table as regular budget expenditures, which accounts for an apparently negative expenditure figure from the WHO Special Account in 1964.

eradication between 1957 and 1967, and US$1000–1200 million over the succeeding 8 years (United States Agency for International Development, 1983).

In its organization and relationship to other public health activities the malaria eradication programme resembled the *Aedes aegypti* eradication programme in Brazil, as it called for a distinct and separate malaria eradication service which would have no other duties. In most countries, the malaria programmes were by design entirely independent of the health authorities, reporting only to a national council and thence to the head of state. The WHO Expert Committee on Malaria (1957) saw the malaria eradication staff as serving eventually as a nucleus for other public health programmes, but believed that it should not merge with other activities until success had been achieved. There were some grounds for this view, because the nature of the field work—namely, house-to-house visits and insecticide spraying—differed from that normally carried out by health staff. Moreover, many more field staff were required for malaria eradication than for any other health programme involving field activity. Indeed, in some countries, malaria eradication staff eventually outnumbered the personnel of all other government health programmes combined.

In addition, malaria eradication staff were generally of higher calibre than other comparably trained health workers and their pay scales were almost always higher. It was inevitable, therefore, that the all but autonomous, independent malaria eradication services, with their more highly paid and better supported staff, would be resented by those in the health services—and they were. As a consequence of this programme, there gradually arose a belief, held with almost ideological fervour, that a "vertical" programme—i.e., virtually any organized programme in which staff were responsible for attaining objectives specific to a particular disease—was a heresy. Later efforts to develop smallpox eradication programmes, even though as an integral part of the health service structure, were often met with hostility; the assistance or even passive cooperation of the malaria eradication services was obtained only with the greatest difficulty, or not at all.

The systematic application of DDT to the walls of all houses and buildings was the principal element in the strategy, although this was supplemented in the later phases of each campaign with the treatment of cases

Table 9.3. Expenditure[a] of funds placed at the disposal of WHO from all sources, for all purposes, for malaria eradication, 1955–1970; for smallpox control, 1955–1958; and for smallpox eradication, 1959–1970 (thousands of US$)

Year	WHO regular budget			All funds at disposal of WHO[b]		
	Total	Malaria	Smallpox	Total	Malaria	Smallpox
1955	9 275	119	9	17 441	2 402	47
1956	9 983	420	5	18 451	3 870	79
1957	12 091	533	13	21 142	9 673	79
1958	13 237	528	30	28 016	13 664	113
1959	14 655	533	0	30 636	13 353	64
1960	16 624	511	60	33 126	13 729	320
1961	19 202	250	33	38 064	14 553	179
1962	24 165	2 409	61	45 659	13 903	297
1963	29 784	4 404	84	54 803	13 247	292
1964	33 869	5 699	75	58 505	13 269	542
1965	38 346	4 701	100	63 124	12 652	233
1966	43 440	5 207	112	72 354	13 191	426
1967	51 340	6 218	2 396	80 557	14 195	3 117
1968	55 563	6 661	2 729	89 940	14 350	3 101
1969	61 687	6 871	2 890	95 172	13 682	3 207
1970	67 191	5 427	2 988	107 530	10 849	3 425
Summary totals[c]						
1955–1958	44 586	1 600	57	85 050	29 609	318
		(3.6%)	(0.1%)		(34.8%)	(0.4%)
1959–1966	220 085	23 714	525	396 271	107 897	2 353
		(10.8%)	(0.2%)		(27.2%)	(0.6%)
1967–1970	235 781	25 177	11 003	373 199	53 076	12 850
		(10.7%)	(4.7%)		(14.2%)	(3.4%)

[a] Source: see Table 9.2.

[b] Identified in the *Official Records of the World Health Organization* as the "integrated international health programme". This includes disbursements under the regular effective working budget, the technical assistance component of UNDP, the Voluntary Fund for Health Promotion and other funds administered by WHO, including funds in trust, Revolving Sales Fund, Real Estate Fund, etc. It does not include bilateral aid.

[c] 1955 was the first year of the global malaria eradication programme; 1959 was the first year of the global smallpox eradication programme; 1967 was the first year of the Intensified Smallpox Eradication Programme.

with drugs. Traditional methods of mosquito control, such as the drainage and larviciding of breeding sites, were rarely used; nor was the need foreseen for research to identify alternative control measures. It was believed that the tools needed for eradication were available; the problem was the administrative one of applying them properly. Thus, for each country, a highly elaborate plan of operations was developed which included the use of standardized and detailed manuals. National plans varied little from country to country. They called for *preparatory*, *attack*, *consolidation* and *maintenance* phases—terms which many persons were later to apply to stages of the smallpox eradication programme.

In summary, during the *preparatory* phase, information was collected on malaria prevalence and vector bionomics, detailed maps were prepared of all structures to be sprayed, houses were numbered, supplies were procured and personnel were recruited and trained. During the *attack* phase, lasting 3–5 years, insecticide spraying teams sprayed the interior walls of all buildings semi-annually with DDT, working block by block and house by house. Late in this phase, case detection was begun by surveillance agents, who visited each house at monthly intervals to take diagnostic blood samples from anyone who had had fever during the preceding month. Presumptive drug treatment was given and additional spraying conducted when infected foci were detected. When the malaria rate fell below 1 case per 1000 persons, the *consolidation* phase began, during which routine spraying was halted and intensive surveillance was conducted to detect the few remaining cases, who were then treated, while any residual foci were eliminated by further spraying. The *maintenance* phase commenced when there had been no evidence of malaria transmission for 3 years. Only in this final phase, expected to be reached within 6–10 years, would the established health services of the country play a role. So detailed and specific were the plans that special manuals were prepared to define explicitly the terminology to be used.

Until 1966, the malaria campaign made steady progress, at least when viewed from a global perspective (Fig. 9.1; Scholtens et al., 1972). Of the total population living in malarious areas in 1959, 26% lived in maintenance- or consolidation-phase areas; by 1966, this proportion had risen to 59%. Most of the progress, however, was made in countries in which rapid economic development was taking place or in which year-round vector breeding did not occur. In other areas, progress was generally less than anticipated, and the financial resources required to sustain unexpectedly protracted attack and consolidation phases of the campaign were far greater than had been foreseen.

By 1966, government authorities and donors alike had become increasingly concerned about the programme's progress and apprehensive about its future. The WHO Expert Committee on Malaria, in its thirteenth report, did not dispel these anxieties. In an analysis of 42 programmes, the Expert Committee reported that in 12, satisfactory progress was being made; in 22, progress was slow and corrective measures had been delayed or were inadequate; and in 8, such measures had been ineffective or had not been taken at all (WHO Expert Committee on Malaria, 1967).

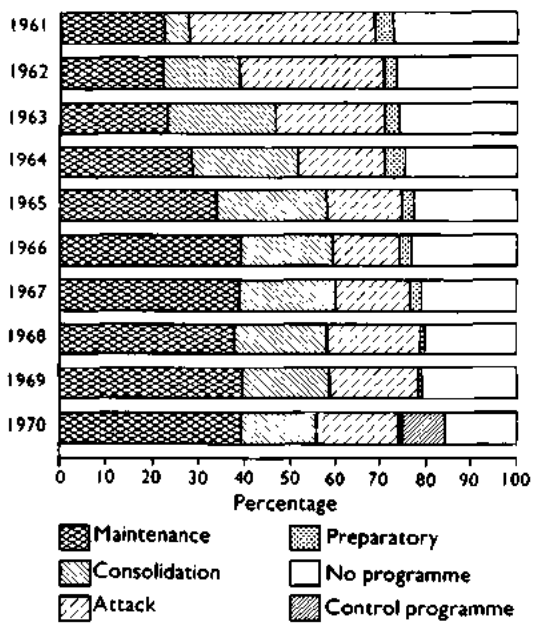


Fig. 9.1. Percentage of population in malarious areas, by phase of campaign, 1961–1970. In 1970, the total population of the malarious areas was 1 801 631 000. (Source: Scholtens et al., 1972, and WHO data.)

In 1967, the Director-General was requested by the Twentieth World Health Assembly in resolution WHA20.14 to study how best to re-examine the global strategy and to report back. His report in 1969 documented a litany of operational, technical, planning and budgetary problems and concluded that:

"The present methods of eradication ... are still laborious and often too expensive for the limited resources of developing countries. Unless the present methodology is further simplified, global malaria eradication, though theoretically possible, will continue to be beyond reach for many years to come." (World Health Organization, 1969b.)

A revised strategy called for malaria control where and when eradication could not be achieved quickly. Global eradication remained the ultimate goal, however, and the responsible division in WHO continued to be called the Division of Malaria Eradication. The principal donors, UNICEF and the United States Agency for International Development (AID), viewed the situation otherwise, and between 1970 and 1973, phased out their support. Dr Perez Yekutiel identifies 1973 as the year that marked the end of the global malaria eradication programme (Yekutiel, 1981).

A fundamental weakness in the strategy had been its almost total reliance on the use of residual DDT within the framework of a rigidly defined, meticulously executed programme. However, as Dr Scholtens and his colleagues (1972) pointed out:

"There is now wide recognition and acceptance of the limitations of short-term national malaria eradication efforts based on residual insecticides ... The use of diverse anti-malarial measures has been strongly recommended, but the development of these has been inhibited for a decade because of high expectations from the eradication effort ... These developments are further complicated by the diminishing number of 'malariologists' and proliferation of 'eradicationists'."

In brief, research on alternative strategies had been seriously neglected (Farid, 1980). Jeffery (1976) pointedly observed:

"The *science* of malaria control, developed slowly and painfully from the beginning of the century to a relatively high state of sophistication, was almost overnight converted to the rather simplistic *technology* of malaria eradication, which basically

required that one know how to deliver 2 grams of something to every square metre of a sometimes elusive interior wall, and to manage a hopefully ever-diminishing Kardex file of cases."

As many individuals wryly noted, the programme was far more successful in eradicating malariologists than malaria (McGregor, 1984).

As is apparent from this brief account, the proposal by the USSR in 1958 for a global smallpox eradication programme coincided with the initial thrust in the development of the global malaria eradication programme. Substantial resources for that programme continued to be both needed and provided throughout the early 1970s. During this period, interest in, and support for, yet another eradication programme was understandably less than enthusiastic. During the mid- to late 1960s, as the increasing difficulties in executing the malaria programme became evident, confidence in the technical judgement and administrative competence of WHO steadily eroded. Not surprisingly, this was reflected in attitudes towards, and support for, smallpox eradication on the part of potential donor agencies, both international and national, as well as those in the endemic countries. Although some of the people concerned with malaria eradication were later to attribute the demise of that programme to the diversion of attention and resources to smallpox eradication in 1967 (Farid, 1980), it is apparent that the malaria eradication effort was by then already in serious difficulty.

Nevertheless, the malaria eradication programme indirectly made major contributions to the development of the successful Intensified Smallpox Eradication Programme by demonstrating the fallacy of two premises. The first was that, given a highly effective control measure, the problem was simply to apply it correctly. For this reason, and contrary to the practice in malaria eradication, WHO smallpox eradication programme staff actively promoted a gamut of research activities which indeed proved crucial to its success. The second premise was that rigidly standardized procedures, uniformly applied throughout all the countries concerned, could be successful. Thus, in the smallpox eradication programme, principles, rather than a detailed methodology, were stressed, and programme staff were encouraged to adapt their programmes to local conditions, to learn from experience and continually to modify their methods. Not surprisingly, programmes in the different countries varied significantly from one another, and a cadre of experienced smallpox epidemiologists proliferated and matured.

The malaria eradication services themselves, with spraymen and surveillance agents regularly visiting every house, might well have contributed significantly to smallpox eradication through their participation in case detection and vaccination. However, as described in later chapters dealing with field operations, in all but a few countries these services refused to undertake any activities except those concerned with malaria. Indeed, in Ethiopia, malaria staff successfully blocked the development of the smallpox eradication programme until 1971.

The yaws programme

Apart from the global programme for malaria eradication and the *Aedes aegypti* eradication programme in the Americas, the only other commitment to disease eradication by an international organization before 1959 pertained to yaws. A resolution committing the Pan American Sanitary Bureau to yaws eradication followed successful yaws control field trials in 1948–1949 in Haiti, long a highly endemic area. This stemmed from the discovery that a single injection of long-acting penicillin provided a cure for this disease, which primarily affects people living under crowded, poverty-ridden conditions in the rural tropics of Asia, Africa and South America. It is caused by a spirochaete, *Treponema pertenue*, which is transmitted by direct, non-sexual contact from person to person, and produces chronic, deforming, and incapacitating lesions. In 1948, UNICEF and WHO began to provide support for mass treatment programmes for syphilis and other treponematoses such as yaws (Guthe, 1960), and over the succeeding decade supplies and equipment worth more than US$9 million were made available to 61 countries and territories. In the yaws eradication programmes, individual patients were diagnosed by inspection and given penicillin, or, where the disease was widespread, the entire population was treated. The results were immediate and dramatic, but the elimination of the disease from an entire area required repeated visits to ensure that all cases had been cured. If any remained after the campaign had ended,

the disease resumed its spread. Occasional latent infections and patients who subsequently relapsed were especially troublesome.

Although a commitment to global eradication was never made by the World Health Assembly, the WHO Expert Committee on Venereal Infections and Treponematoses (1960) recommended that "there should be no delay by health administrations in extending the campaign for the world-wide eradication of yaws and endemic syphilis which is a feasible undertaking from a technical point of view". Programmes designed to achieve country-wide eradication were launched in the mid-1950s in 49 countries and were remarkably successful in controlling yaws; however, the disease was eliminated in only a few of the smaller countries (Yekutiel, 1981). Evaluations revealed far more low-level persistent infection and transmission than had been originally supposed and by 1966–1967 the term eradication was no longer applied. Even in the Americas, in which regional eradication was the stated objective, the programme was not vigorously supported and Haiti itself never became completely free of yaws.

Programmes for the eradication of other diseases

The possibility of eradicating a number of human diseases was actively debated in many different forums from 1947 onwards. Such discussions, however, effectively ended in 1966, at about the time that the Intensified Smallpox Eradication Programme was established, and simultaneously with an increasing awareness that none of WHO's regional or global programmes offered much hope of success. In the USA, the term eradication and the concept were examined and discussed with regard to several other diseases. In 1961, the Surgeon General of the United States Public Health Service established a special task force "to evaluate present efforts to control syphilis and to recommend principles and methods that will make it possible to establish a timetable leading to the eradication of syphilis as a public health problem" (Hinman, 1966). The task force, more circumspect, recommended a programme to "eliminate syphilis as a public health hazard in the United States", but little came of this. The idea of eradicating tuberculosis was more forcefully pursued, first with Dr J. E. Perkins (1959) and then with Dr Soper (1962) arguing that a global programme should be undertaken. Dr Soper took the same view about tuberculosis as he had about other diseases—namely, that the problem was fundamentally one of political commitment and public health administration. The Surgeon General, in 1963, established a task force to examine this problem as well, but its report provided no blueprint for eradication (Hinman, 1966).

During the 1960s, the basic concept of eradication increasingly fell into disrepute. One of the last of the papers to advocate it was that by Dr Soper entitled "Rehabilitation of the eradication concept in prevention of communicable diseases" (Soper, 1965). Most persons accepted the views of the widely read Dr René Dubos, who eloquently described for layman and scientist alike the intricate adaptive relationships, evolved over time, between man and microorganisms. One of his books, *Man Adapting*, published just before the advent of the Intensified Smallpox Eradication Programme, concludes that eradication programmes "will eventually become a curiosity item on library shelves, just as have all social utopias".

Following the success of the smallpox eradication programme, however, the concept of eradication again came under examination, and although some scientists waxed enthusiastic about the prospects of eradicating other human diseases (Stetten, 1980)—notably, poliomyelitis, measles (Hopkins et al., 1982), yaws (Hopkins, 1976) and dracunculiasis (Hopkins, 1983b)—others, who had themselves been intimately involved with earlier eradication programmes, concluded that there were no suitable candidate diseases for global eradication in the immediate future (Henderson, 1981; Yekutiel, 1981). Nevertheless, in view of the unexpectedly rapid progress that had been made in the control of poliomyelitis in the Americas, the Directing Council of the Pan American Health Organization accepted in 1985 a "proposal for action" for the eradication of poliomyelitis from the Americas by 1990. The following year, in 1986, the Twenty-ninth World Health Assembly endorsed efforts to eliminate dracunculiasis "country by country, in association with the International Water Supply and Sanitation Decade" (World Health Organization, 1987). The resolution (WHA39.21) of the Health Assembly refers to "eliminating" the disease, but it is difficult to distinguish this from the notion of eradication (see Chapter 31).

Eradication as Viewed by a Distinguished Scientist

"Eradication in its most exacting sense, namely as applied to the whole world, is not merely an armchair game of epidemiologists; it has become the official policy of several national and international organizations.

"At first sight, the decision to eradicate certain microbial diseases appears to constitute but one more step forward in the development of the control policies initiated by the great sanitarians of the nineteenth century, which have been greatly expanded since the beginning of the microbiological era. In reality, however, eradication involves a new biological philosophy. It implies that it is possible and desirable to get rid of certain disease problems of infection by eliminating completely the etiological agents, once and for all ...

"In all cases the problems posed by the biological and epidemiological peculiarities of each type of infection are still further complicated by financial, administrative and political uncertainties. Even if genuine eradication of a pathogen or vector on a worldwide scale were theoretically and practically possible, the enormous effort required for reaching the goal would probably make the attempt economically and humanly unwise ...

The popular appeal and fervid ring of the word eradication is no substitute for a searching analysis of the manner in which limited supplies of resources and technical skills can best be applied for the greatest social good ...

"Social considerations, in fact, make it probably useless to discuss the theoretical flaws and technical difficulties of eradication programs, because more earthy factors will certainly bring them soon to a gentle and silent death. Certain unpleasant but universal human traits will put impassable stumbling blocks on the road to eradication. For example, it is easy to write laws for compulsory vaccination against smallpox, but in most parts of the world people would much rather buy the vaccination certificate than take the vaccine; and they shall always find physicians willing to satisfy their request for a small fee ...

"Public health administrators, like social planners, have to compromise with the limitations of human nature. For this reason, and many others, eradication programs will eventually become a curiosity item on library shelves, just as have all social utopias." (From *Man Adapting*, by Dr René Dubos, 1965.)

WHO SMALLPOX CONTROL AND ERADICATION ACTIVITIES, 1946–1958

Introduction

Prior to 1959, when the Twelfth World Health Assembly decided to undertake smallpox eradication, the only cooperative international effort to control smallpox was a WHO regional programme to eradicate it in the Americas. That programme, begun in 1950, was not vigorously promoted and, by 1959, was progressing far more slowly than had been hoped (Pan American Health Organization, 1959).

It may seem curious that smallpox was not identified by WHO as the initial target for eradication, if indeed the objective of disease eradication was to be pursued at all. Smallpox, after all, could easily be prevented by vaccination, and many industrialized countries as well as some developing ones had demonstrated the feasibility of interrupting transmission over large areas encompassing several countries. Because of the frequency of importations, the disease was of concern to all countries and vaccination was extensively practised. Even as late as the 1970s, smallpox vaccine was the only vaccine widely used throughout the world. For tropical areas, a heat-stable freeze-dried preparation was available, although not widely used (see Chapter 7). It was recognized that the disease was spread through close personal contact and that there was no known animal reservoir. Transmission by insect vectors, if it occurred at all, was of no significance.

The control and eventual eradication of smallpox depended in large part on the effective vaccination of large numbers of people. This was a much simpler operation than the more complex and costly vector control measures needed, for example, for the

eradication of yellow fever or malaria, and was much easier than trying to treat all cases of a disease—the basic strategy employed in yaws and hookworm eradication programmes.

As has been noted, however, the historical roots of human disease eradication programmes go back to Dr Gorgas' successful elimination of yellow fever from Cuba and Panama—basically a vector control programme—followed by the Rockefeller Foundation's yellow fever eradication programme. When this was unsuccessful, the objective of *Aedes aegypti* eradication was pursued throughout Brazil and subsequently other Latin American countries. During this time, too, recently introduced infestations of *Anopheles gambiae* in Brazil and Egypt were eliminated. All these activities involved the allocation of large resources to vector control. The question of eradicating smallpox did not arise, perhaps in part because most of those concerned with the eradication concept worked in Brazil and the USA, in which the mild form of the disease, variola minor, prevailed—an illness of marginal public health importance; and perhaps in part because smallpox was then so widespread.

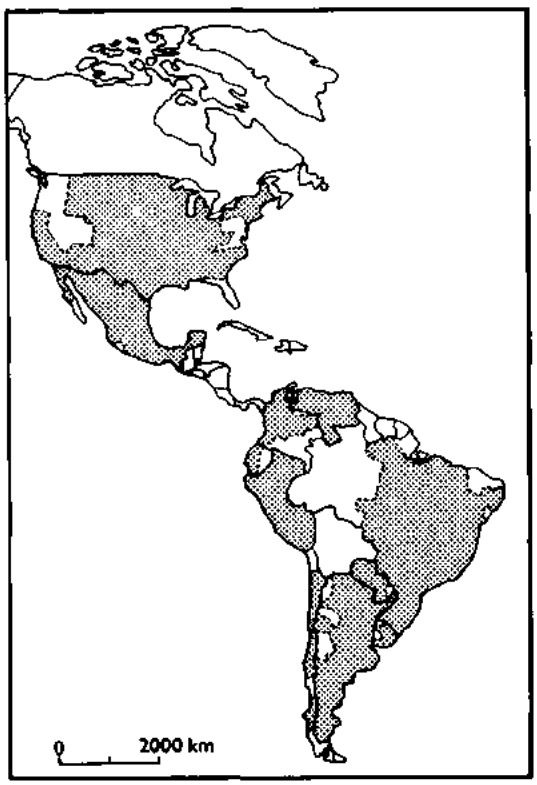
During and immediately after the Second World War, the all but miraculous effect of DDT in destroying insect vectors of disease promised an ultimate solution to the serious problem of malaria. Senior staff of WHO and of the national health services in many countries had been initiated into public health work either in pre-war vector control programmes (principally in the Americas) or in post-war malaria control programmes, and this was where their interest lay. The promise of DDT was still to be explored—a new and exciting venture, incomparably more attractive than endeavouring to apply more widely a vaccine that had been in use for 150 years in the control of a disease that, owing to importations, continued to recur everywhere.

The decision, in 1959, to commit WHO to the global eradication of smallpox represented for the World Health Assembly a marked departure in its attitude towards this disease. Before this time, the Health Assembly resolutions had cautiously urged only improved programmes for smallpox control; for example, in 1954, in resolution WHA7.5, it had requested the Director-General "to provide within budgetary limitations the assistance requested by national administrations to further their smallpox control programmes" (World Health Organization, 1973a). During this period, the Organization's activities pertaining to smallpox had been concerned primarily with the implementation of the International Sanitary Regulations, the technology required for the preparation of a suitable freeze-dried vaccine, and the development of vaccine standards which might be adopted internationally (see Chapter 7).

Smallpox Eradication in the Region of the Americas

In the Region of the Americas, WHO's interest in smallpox had been greater than in its five other regions. The countries of that region, on the recommendation of the Regional Director, Dr Soper, had unanimously agreed in 1950, at the XIII Pan American Sanitary Conference, to undertake a regional programme for the eradication of smallpox, a disease which was described in the Director's report as being widespread throughout the Americas at that time. In Fig. 9.2, which identifies administrative subdivisions in the region that reported 1 case or more during a 3-year period, the problem appears to be far more extensive than it really was. In the USA, for example, cases were almost all of the mild variola minor type; no state reported more than a few cases, and almost none of them was confirmed as smallpox by the state health authorities. Whatever the true extent of the problem, the delegates were sufficiently persuaded to decide on a regional eradication programme, and in 1952 they voted to allocate US$75 000 to the programme; an additional subvention of US$144 000 was made available in 1954.

The ability and inclination of the Region of the Americas to adopt policies dissimilar to those of the Organization as a whole is partly explained by the fact that this region historically had a somewhat different relationship to WHO from that of the other regions, being rather more independent and having additional financial resources. When, in 1946, an International Health Conference had drawn up the WHO Constitution, it had been envisaged that regional organizations then in existence would become an integral part of WHO and, specifically, that the Pan American Sanitary Bureau (PASB) would be integrated as soon as possible. PASB, then only a small organization with few staff, had been in



"SMALLPOX: This map is... prepared on the basis of routine reports received at PASB. It shows the States, Departments or Provinces where one or more cases of the disease were reported [between January 1947 and May 1950]. It is very probable that some of the shaded areas may have had only a few cases of smallpox and that these may have been infected in other areas.
"No reports were received from Bolivia where smallpox is known to occur. Smallpox cases in Cuba, Panama, Trinidad and the Chilean epidemic, were of imported origin. No cases were reported in Haiti, Dominican Republic, Costa Rica, El Salvador and Honduras...
"No distinction has been made between smallpox and alastrim." (Pan American Sanitary Organization, 1950b.)

Fig. 9.2. States, departments or provinces of countries in the Americas that reported smallpox cases to the Pan American Sanitary Bureau, January 1947 to May 1950.

existence, under one name or another, since 1902 (see Chapter 12). Its primary concern, like that of several other regional health bodies, had been to formulate agreements relating to the quarantinable diseases and to oversee their implementation (Howard-Jones, 1980). However, in January 1947, at the XII Pan American Sanitary Conference, the delegates emphasized the separate identity of PASB by constituting the Pan American Sanitary Organization (PASO; the name was changed in 1958 to the Pan American Health Organization, or PAHO) with PASB as its headquarters and secretariat. Nine months later, at the first meeting of its Directing Council, it authorized its Executive Committee to negotiate with WHO on condition that "the Pan American Sanitary Organization should continue to function as an independent entity for the solution of problems of a continental character" (Pan American Sanitary Organization, 1950a). In April 1949, Dr Brock Chisholm, Director-General of WHO, and Dr Soper, the Director of PASB, signed a formal agreement which recognized PASO as an "independent entity" which could carry out and finance its own programmes in the Western Hemisphere provided that they were "compatible with the policy and programmes" of WHO (Howard-Jones, 1980). PASB was funded thereafter from two sources: funds provided through WHO from the assessed contributions of its Member States and additional funds contributed by Member countries of PASO, the largest contributor being the USA. With proportionately more funds than WHO and with a forceful director committed to the concept of eradication, PASO embarked on a regional smallpox eradication programme in 1950, in addition to the other eradication programmes already described.

Until 1947, Dr Soper had personally exhibited little interest in smallpox (Soper, 1965). That year an outbreak of 9 cases occurred in New York City, introduced by a visitor arriving by bus from Mexico (Weinstein, 1947). To control the outbreak, an ill-advised, chaotic, month-long mass vaccination campaign had been launched during which 6.3

million persons were vaccinated, 6 of whom died from complications of vaccination (Greenberg, 1948). Dr Soper, learning that thermostable freeze-dried vaccine was being produced in Europe, recognized that such a vaccine might make it possible to eradicate smallpox in the Americas. Moreover, in the light of the recent turmoil of the New York City outbreak, an eradication programme could be seen to be of significant benefit to PASO's largest contributor, the USA. The programme would also serve to demonstrate the value of PASO as an international health agency of relevance to all Member countries in a way that programmes of little significance to the USA, such as those for the eradication of yaws, yellow fever and malaria, would not. As Dr Soper noted: "The point is too often missed by public health administrators that theirs is a selling as well as an administrative job" (Soper, 1965).

Dr Soper sought help from the United States National Institutes of Health in developing the techniques for preparing freeze-dried smallpox vaccine and was referred to Mr William Gebhardt at the Michigan State Health Department Laboratory. By 1950, studies on a new freeze-dried vaccine, prepared by Mr Gebhardt, commenced in Peru under the direction of a new PASB staff member, Dr Abraham Horwitz, later to become Dr Soper's successor. The results were excellent and soon thereafter Mr Gebhardt, supported by PASB, assisted laboratories in other countries of the Americas in preparing the vaccine. Arrangements were made to have it tested at a laboratory in Denmark, although this was seldom done (Pan American Health Organization, 1966). PASB offered technical assistance to some countries but, as noted in the Director's annual report for 1957 (Pan American Sanitary Organization, 1958): "The Bureau did not have the funds nor the appetite for joining in the intensive vaccination campaigns that have so often given temporary relief, but became interested rather in improving the tools and methods through which permanent eradication might be brought about." Thus, responsibility for the execution of national programmes and for their cost was left essentially to the respective governments. From available records, it would appear that the programmes in the various countries differed widely in quality; vaccinial immunity after mass campaigns was seldom assessed and little was done to improve the reporting of smallpox cases. The Director, in his annual report for 1958 (Pan American Health Organization, 1959), characterized the programme "as advancing at a slower rate than had been anticipated" and noted that "the disease is still an important public health problem in the Americas". Nevertheless, by the end of 1958, smallpox transmission appeared to have been, or to be on the verge of being, interrupted in all the countries of the Americas except Brazil, Colombia and Ecuador (see Chapter 12).

Table 9.4. Expenditure by PAHO for smallpox eradication, 1953–1966 (US$)

Year	Amount
1953	11 126
1954	15 099
1955	38 363
1956	74 462
1957	66 373
1958	45 218
1959	43 364
1960	32 919
1961	42 966
1962	27 428
1963	20 622
1964	23 001
1965	32 486
1966	184 700

Source: Financial records of PAHO.

Up to 1966, the amounts spent annually by PAHO on smallpox eradication never exceeded US$75 000 (Table 9.4). The investment was modest in relation to the results obtained.

An Abortive Attempt to Launch a Global Smallpox Eradication Programme, 1953

At the World Health Assembly, the eradication of smallpox was discussed for the first time in 1953. The Constitution of WHO states in Article 2(*g*) that one of the functions of the Organization is "to stimulate and advance work to eradicate epidemic, endemic and other diseases". Citing this article, Dr Chisholm, then serving his last year as WHO's first Director-General, presented a special report entitled "Further action on general world health problems" (document EB11/63; unpublished) to the eleventh session of the Executive Board in February 1953 and then to the Sixth World Health Assembly in May. The report states:

"The first four years of work by WHO have shown its programmes developing in practice into two almost distinctive groups. Firstly there are the

essential programmes of general international character, many of them traditional ... [such as] ... quarantine, statistical and standardization of drugs ... Secondly, there are the advisory services provided directly to individual governments ...

"Inevitably the form of the advisory services in the first phase has been determined almost entirely by local needs ... Originally the Interim Commission and the Health Assembly ... visualized that the Health Assembly would define true world programmes into which the country requests would be incorporated."

Dr Chisholm noted that a general, direct, practical world programme would demonstrate "the importance WHO has for every Member State" and also its role "not only through the necessary and valuable present form of direct assistance to governments, but also by concerted international action". He took note of the smallpox eradication programme in the Americas and advanced the argument that an appropriate subject of general concern should be selected for a world-wide campaign—specifically, smallpox eradication. A 5-year budget providing approximately US$131 000 per year was proposed.

The proposal was not enthusiastically received. Delegates from Australia, Belgium, El Salvador, India, Pakistan, South Africa, the United Kingdom, the USA and Venezuela all expressed views to the effect that the problem of smallpox was really a regional or even local one, and that insufficient knowledge was available. Summarizing, the delegate of the United Kingdom pointed out that the problem was vast and complicated and it did not appear that a world-wide machinery for such a campaign was suitable at this time. He pointed out that, "Such a campaign might prove uneconomical and would not ... add to the prestige of the Organization" (World Health Organization, 1953). He put forward a resolution which read, in part:

"In view of the many political, economic and social factors that must be considered,

REQUESTS the Executive Board to further study [the matter] and to report to the Seventh World Health Assembly."

The delegate of France offered an alternative resolution which stated, *inter alia*:

"Approves in principle the suggestion of the Director-General that WHO should encourage certain world-wide programmes."

This was rejected, and a somewhat amended version of the United Kingdom draft was adopted as resolution WHA6.18 (World Health Organization, 1973a).

Each of the regional committees was asked to discuss the proposal but, except in the Americas, none expressed enthusiasm and, at the Seventh World Health Assembly in 1954, the proposal was deferred pending further study. Later that year, the newly elected Director-General, Dr Marcolino Candau, sent a letter to all Member States offering advice and assistance, if required, in the execution of smallpox control programmes and requested replies. In his report (document A8/P&B/7; unpublished) to the Eighth World Health Assembly in 1955 Dr Candau said that the replies received indicated that most countries "do not desire any immediate practical assistance in the control of smallpox. A small number would welcome technical advice and assistance, mainly in connection with the production of reliable [freeze-]dried vaccine. Only two requests were made for consultant services". The concept of a global programme for smallpox eradication was thereupon quietly buried. In that same year, however, the proposal to adopt a policy of

WHO, c 1950

Plate 9.5. Brock Chisholm (1896–1971), the first Director-General of WHO, 1948–1953, proposed to the World Health Assembly in 1953 that a programme of global smallpox eradication should be undertaken by WHO. Considered then by delegates to be too "vast and complicated", the initiative was rejected, not to be reconsidered until 1958. Meanwhile, a programme was started in 1955 for the global eradication of malaria.

global malaria eradication was advanced and delegates urged that it should be undertaken as a matter of the highest priority. The programme, which was vastly more costly and complex than smallpox eradication and whose feasibility was far more questionable, was adopted virtually without dissent.

Not until the USSR returned to active participation in WHO and Professor Zhdanov presented its proposal was the subject of smallpox eradication again raised. Although the decision in 1959 to embark on a global eradication campaign might appear to have been a logical extension of the regional eradication programme in the Americas, it was not. Professor Zhdanov himself was unaware of the regional initiative and it was not mentioned in debate either at the Executive Board sessions or at the World Health Assemblies of 1958 and 1959, nor was it noted in the Director-General's reports. It was a regional programme which, by 1958, had been largely forgotten, even by delegates of the countries of the Americas.

THE SMALLPOX ERADICATION PROGRAMME, 1959–1966

Introduction

Seven years had elapsed between the decision of the Twelfth World Health Assembly (1959) to undertake global smallpox eradication and that of the Nineteenth World Health Assembly (1966) to allocate significant funds from the regular budget of the Organization to enable an intensified campaign to be conducted. Progress during this period was far slower than had been anticipated in the Health Assembly resolution WHA11.54. During the period 1959–1966, malaria eradication was WHO's largest programme and its principal preoccupation, and this was no less true even for many Member States in which smallpox was endemic, because malaria was also present in most of them. WHO allocated some funds for smallpox eradication, intercountry meetings were held to discuss programme execution and methods of vaccine production, and letters were sent periodically by the Director-General appealing to Member countries for voluntary donations of vaccine. Few such donations were received. The USSR, under bilateral agreements, provided large quantities of vaccine to India, as well as to a number of other countries, and the USA provided bilateral support to several smallpox eradication programmes, including those of Bolivia, India and Iran, but on the whole enthusiasm for smallpox eradication was lacking.

Greater interest in the programme began to be shown when a series of events led the USA, in 1965, to commit itself to providing assistance to a regional smallpox eradication programme in western and central Africa, and to begin to support more enthusiastically the programme for global smallpox eradication. The USSR, impatient with the inadequacy of a programme in which it rightly took a proprietary interest, eagerly welcomed this change in attitude. In concert with other delegations, it requested the Director-General, in 1965, to prepare a proposed programme and budget for an intensified campaign. In 1966, this was approved together with a designated financial commitment of US$2.4 million from the regular budget. Preparations thereupon started for an Intensified Smallpox Eradication Programme to begin in January 1967.

Status of Smallpox, 1959

In 1959, 63 countries or territories officially reported to WHO a total of 77 555 cases of smallpox. When national records were reviewed and revised by WHO in the late 1960s, the total for 1959 was increased to 96 571 cases but, whatever the figures, reporting was recognized to be incomplete, though the degree of underreporting was not known. Some countries provided no reports despite the stipulations of the International Sanitary Regulations; in other countries, including large ones with comparatively well-developed health systems, the only cases reported were those hospitalized in the larger cities.

No attempt was made in 1959 to distinguish between countries in which smallpox was endemic and those in which the only cases were imported ones; in preparing this chapter, however, we have tried to determine the probable situation in 1959, based on information now available (Fig. 9.3 and Tables 9.5 and 9.6). To facilitate comparison with the situation in the period 1967–1977, the designations of countries and territories as they existed in 1977 are used. From the records, it is probable that smallpox was endemic in 1959 in 59 countries and territories in Africa, South America and Asia, which

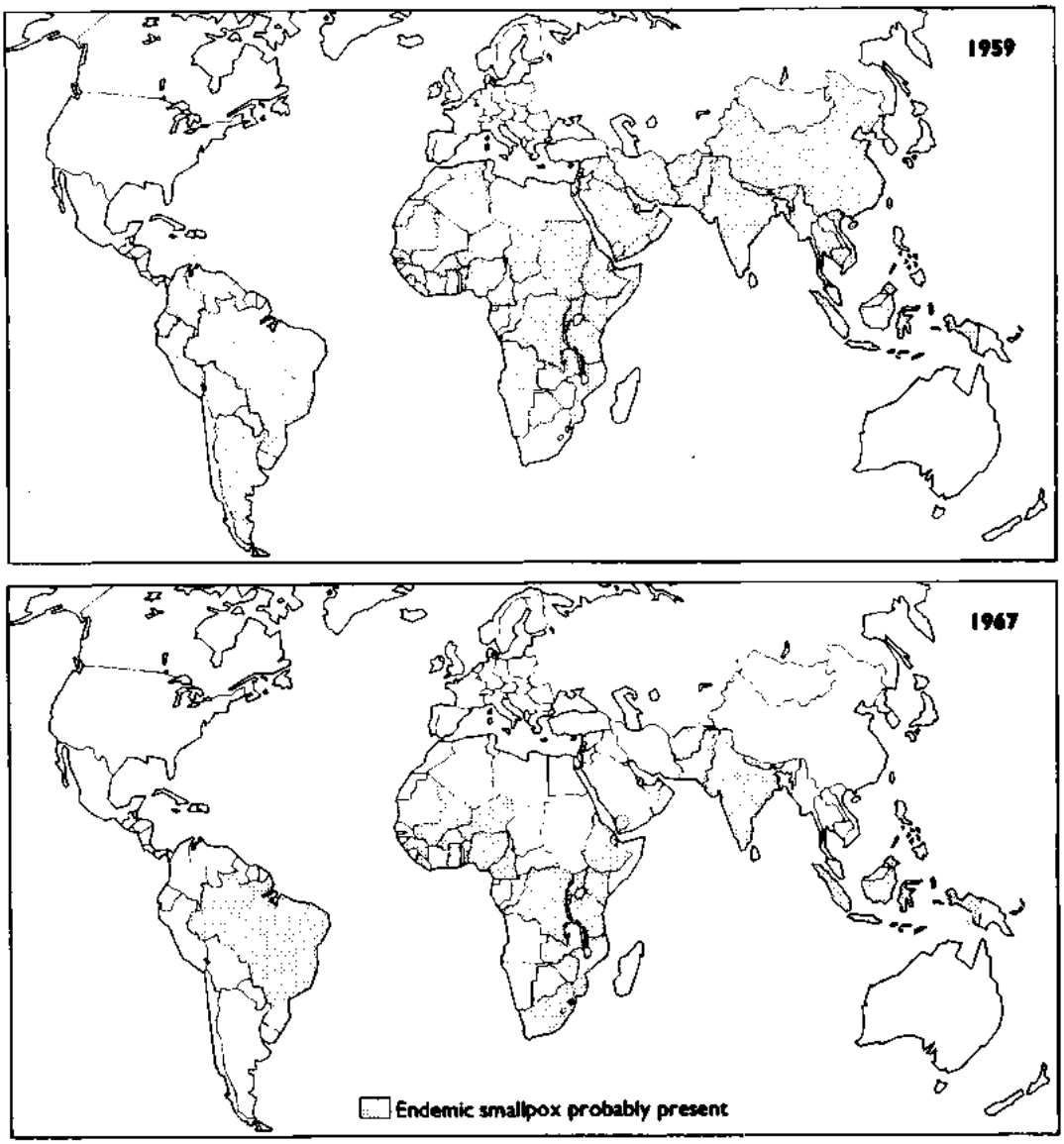


Fig. 9.3. Countries and territories in which smallpox was believed to be endemic, 1959 and 1967.

then had a total population of 1 734 921 000. Together, these countries constituted a substantial proportion of the land area of the 3 continents concerned and included 59% of the world's population. It is important to note, however, that in 1959 endemic transmission was on the verge of interruption in a number of Asian countries (Cambodia (Democratic Kampuchea), China, Iraq, Malaysia, Saudi Arabia, Thailand and Viet Nam) and in Africa (Algeria and Angola). Transmission appears to have been interrupted in all these countries over the period 1959–1962.

The Global Eradication Programme Begins, 1959

The Director-General's proposed programme, as presented to the Twelfth World Health Assembly in 1959, envisaged national campaigns in which at least 80% of the population of each country would be vaccinated or revaccinated. Responsibility would rest primarily with individual governments, which would be expected to bear the major burden of programme administration and execution as well as of cost (World Health

Table 9.5. Countries and territories believed to have endemic smallpox, 1959 and 1967: summary by continent

Continent	Countries and territories with endemic smallpox			
	in 1959		in 1967	
	Number	Population[a] (thousands)	Number	Population[a] (thousands)
Africa	34	198 490	23	215 914
Americas	6	115 198	1	88 737
Asia	19	1 421 233	7	774 124
Total endemic	59	1 734 921	31	1 078 775
World population	–	2 958 143	–	3 463 145
Proportion of world population living in endemic areas	59%		31%	

[a] Population data from United Nations (1985).

Organization, 1959b). WHO would be responsible primarily for providing technical assistance when requested and fellowships for the training of staff, as well as for assisting in the development of vaccine production. Little was said about a leadership role for WHO in overall planning or in coordinating the campaign. Since delegates to the 1954 Health Assembly and most regional committees had so forcefully argued the case that smallpox was a local or regional matter, this approach was understandable. Moreover, malaria eradication then commanded whatever discretionary resources were available.

Budgetary Provision for the Programme

The annual expenditure of funds for smallpox eradication between 1959 and 1966 by WHO, PAHO and the United Nations Expanded Programme of Technical Assistance is shown in Table 9.7. Between 1960 and 1965, the annual expenditure by WHO and PAHO ranged from US$76 118 to US$188 351, increasing in 1966 to US$374 544, primarily because of a large disbursement of funds by PAHO for supplies for Brazil. Donations of vaccine averaged US$120 000 per year from 1960 to 1966, and UNICEF provided almost US$250 000 during this period for vaccine production equipment. Overall, however, the expenditure for smallpox eradication amounted to only 0.6% of the total expenditure of funds placed at the disposal of WHO between 1960 and 1966 and to 0.2% of the regular budget in the same period (see Table 9.3).

Every year the Director-General reported to the Health Assembly that progress in the smallpox eradication programme was slow, the principal obstacle being identified as the lack of funds for vehicles, supplies and equipment. The Health Assembly regularly urged that a larger budget should be provided for smallpox eradication and, when this was not done, finally requested the Director-General, in resolution WHA17.43 in 1964, to provide "under the future regular programme and budget of the Organization—if necessary at the expense of lower-priority activities—for making good the shortfall of the vaccine required, and of other essential supplies and equipment . . ." (World Health Organization, 1973a). Apparently, there were few activities of lower priority because the Director-General's proposed budget for 1966 provided for less than US$200 000.

Programme Activities, 1959–1962

Responsibility for coordinating the programme was assigned to a newly recruited medical officer, with a secretary, who were for several years WHO's only full-time employees working on smallpox eradication. The medical officer worked as one of several in the Virus Diseases unit of the Division of Communicable Diseases. For comparison, there were 5 professional staff at Headquarters in the Leprosy unit and 28 in the Division of Malaria Eradication. There were no staff members in any of the WHO regional offices solely responsible for smallpox eradication and, until 1966, only 5 full-time WHO

smallpox eradication advisers were assigned to field programmes—in Liberia, from 1962; Bolivia, from 1963; Afghanistan, from 1964; and Kenya and Mali, from 1965. A WHO adviser served in a part-time capacity in Nepal from 1962. The total population of these countries was less than 40 million. None of the programmes made significant progress, although Bolivia, in which there were no cases of smallpox when the adviser was assigned, remained free of the disease.

Soon after the programme began, inter-regional conferences were held in Africa (1959) and in Asia (1960) to discuss methods of conducting smallpox eradication programmes, and training courses in the techniques of producing freeze-dried vaccine were held in Nigeria (1960) and Thailand (1961). The medical officer from WHO Headquarters visited a number of countries, on request, to discuss the possible implementation of programmes, but it was apparent that few countries were in a position to do much unless additional resources could be made available.

From 1959 onwards, the Director-General, at the request of the World Health Assembly, presented each year a formal report on the programme for discussion by the delegates. Beginning in 1961, the tenor of the discussions and the resolutions reflected increasing impatience. At the Fourteenth World Health Assembly (February 1961), the comments of a delegate of the USSR, Dr V. N. Butrov, were reported as follows:

"It seemed ... that WHO and its regional offices were not giving the problem all the attention that

Table 9.6. Countries and territories in Africa, the Americas and Asia[a] believed to have endemic smallpox, 1959 and 1967

Country[a]	1959[b]	1967[b]	Population 1959[c] (thousands)	Probable year of last endemic cases
Africa[d]				
Benin (Dahomey)	×	×	2 224	
Burundi	×	×	2 876	
Cameroon	×	×	5 441	
Ethiopia	×	×	19 589	
Ghana	×	×	6 473	
Guinea	×	×	3 226	
Kenya	×	×	7 653	
Liberia	×	×	1 025	
Malawi	×	×	3 454	
Mali	×	×	4 544	
Mozambique	×	×	6 446	
Niger	×	×	3 190	
Nigeria	×	×	41 207	
Rwanda	×	×	2 676	
Sierra Leone	×	×	2 444	
Southern Rhodesia (Zimbabwe)	×	×	3 464	
Togo	×	×	1 493	
Uganda	×	×	6 347	
United Republic of Tanzania	×	×	9 769	
Upper Volta (Burkina Faso)	×	×	4 205	
Zaire (Democratic Republic of the Congo)	×	×	17 347	
Zambia	×	×	3 059	
Transmission ceased between 1959 and 1967				
Algeria	×	○	10 574	1961
Angola	×	○	4 738	1959
Botswana	×	○	471	1964
Chad	×	○	3 017	1965
Côte d'Ivoire	×	○	3 673	1966
Djibouti	×	○	123	1959
Equatorial Guinea	×	○	249	1960
Gambia	×	○	369	1966
Mauritania	×	○	960	1962
Senegal	×	○	2 980	1963
Somalia	×	○	2 230	1962
Sudan	×	○	10 954	1962
Transmission resumed between 1959 and 1967				
South Africa	○	×	[17 930]	

it deserved . . . [In] the Annual Report for 1960, for example, the chapter on the Eastern Mediterranean Region was the only one where the matter was dealt with at all seriously. The chapter on South-East Asia . . . and the chapters on Africa and the Americas did not contain any reference to smallpox." (World Health Organization, 1961.)

A delegate of Peru, Dr Carlos Quirós, was no less concerned; he noted that "the proposed programme and budget estimates failed to show any specific allocation for that work [smallpox eradication]". At that time, the budget document, as presented to the delegates, identified project budgets in each country and region, but the amount to be spent by WHO Headquarters on smallpox eradication was not specified as such nor was a table provided to summarize expenditures by categorical programmes. Dr Quirós introduced a resolution calling for a specific budget allocation, arguing that "WHO should not merely give assistance to governments for smallpox eradication but should give it as part of a well-defined global eradication programme like the programme that existed in the case of malaria". The Director-General discouraged such a move, explaining that he did not see what purpose it would serve. The resolution ultimately passed (WHA14.40) stated only that ". . . it is urgent to speed up the activities of the programme. . ." but, for the first time, the Health Assembly specifically called for "voluntary contributions in cash or in kind" from Member States, an appeal which was thereafter renewed annually.

During the first few months of 1962, 13 imported outbreaks occurred in Europe, a fact

Table 9.6 (*cont.*)

Country[a]	1959[b]	1967[b]	Population 1959[c] (thousands)	Probable year of last endemic cases
Americas				
Brazil	×	×	70 468	
Transmission ceased between 1959 and 1967[e]				
Argentina	×	○	20 267	1966
Bolivia	×	○	3 354	1960
Colombia	×	○	15 082	1965
Ecuador	×	○	4 293	1963
Paraguay	×	○	1 734	1960
Asia				
Afghanistan	×	×	9 831	
Bangladesh (East Pakistan)	×	×	50 370	
India	×	×	421 741	
Indonesia	×	×	94 183	
Nepal	×	×	9 254	
Pakistan (West Pakistan)	×	×	48 912	
Yemen	×	×	3 957	
Transmission ceased between 1959 and 1967				
Burma	×	○	21 329	1965
China (People's Republic)	×	○	657 060	1961
Democratic Kampuchea (Cambodia)	×	○	5 309	1959
Democratic Yemen	×	○	1 183	1960
Iran	×	○	19 607	1963
Iraq	×	○	6 649	1959
Malaysia	×	○	7 971	1960
Oman	×	○	495	1962
Qatar	×	○	43	1961
Saudi Arabia	×	○	3 974	1961
Thailand	×	○	26 113	1962
Viet Nam	×	○	33 252	1959
Total population of endemic areas			1 734 921	

[a] Designation of countries and territories as in 1977.
[b] × = endemic smallpox present; ○ = probably not endemic for smallpox.
[c] Population data from United Nations (1985).
[d] Excluding Lesotho, endemic in 1961–1962, and Swaziland, endemic in 1963–1966.
[e] In Peru, endemic transmission ceased in 1954 but resumed in the years 1963–1966.

Table 9.7. Expenditure for smallpox eradication by WHO and PAHO, 1959–1966 (US$)[a]

WHO region and country	1959	1960	1961	1962	1963	1964	1965	1966
Africa								
Intercountry	0	738	2 633	1 455	0	0	30 590	43 744
Côte d'Ivoire	0	0	395	88	0	0	0	0
Liberia	0	0	0	0	19 719	12 893	0	0
Mali	0	0	4 152	0	0	0	7 402	20 094
Americas								
Intercountry	9 961	619	903	8 285	33 384	17 011	4 116	34 539
Argentina	0	0	0	0	0	0	16 343	0
Bolivia	0	0	0	32 390	8 891	13 920	11 343	16 051
Brazil	9 814	0	21 444	0	1 869	0	12 027	152 626
Colombia	33 052	16 041	5 201	0	0	0	0	0
Ecuador	11 270	16 259	15 418	63 525	29 926	22 999	0	0
Honduras	0	0	0	0	0	0	0	2 400
Venezuela	0	0	0	0	22	0	0	0
South-East Asia								
Intercountry	0	1 282	5 617	13 797	22 422	23 889	35 840	23 249
Afghanistan	0	0	0	0	0	15 515	18 069	15 313
Burma	0	0	0	0	0	0	0	160
India	0	0	0	0	0	6 924	20 830	18 807
Nepal	0	0	599	12 880	14 100	14 441	0	17 828
Eastern Mediterranean								
Intercountry	0	15 392	0	0	0	0	0	718
Pakistan	0	0	3 749	7 418	0	4 734	0	0
Egypt (United Arab Republic)	0	0	0	32	6 125	0	0	0
Saudi Arabia	0	0	0	8 530	0	0	0	0
Sudan	0	11 567	87	5 566	6 424	5 244	4 671	0
Yemen	0	0	0	11 438	694	147	0	1 904
Western Pacific								
China (Province of Taiwan)	0	0	0	0	0	0	0	1 500
WHO Headquarters	0	31 174	15 920	3 000	4 000	15 235	27 120	25 611
Total[b]	64 097	93 072	76 118	168 404	147 576	152 952	188 351	374 544
Vaccine[c]	0	65 132	103 352	128 634	105 932	373 954	28 928	33 070
UNICEF[d]	0	162 186	–	–	38 132	15 233	15 692	17 900
Grand total	64 097	320 390	179 470	297 038	291 640	542 139	232 971	425 514

[a] Source: see Table 9.2.
[b] Total includes funds from the regular budgets of WHO and PAHO, the Special Account for Smallpox Eradication (except vaccine) and support provided by the United Nations Expanded Programme of Technical Assistance.
[c] Value of vaccine contributed through the Special Account for Smallpox Eradication.
[d] Costs of vaccine production equipment provided to Burma, Guinea, India, Indonesia, Kenya and Pakistan (East).

pointedly reported to the Fifteenth World Health Assembly by the Director-General. Despite the obvious problem which smallpox constituted for non-endemic countries, he observed that the Organization had received to date only 34 million doses of vaccine, of which 25 million were from the USSR. His report acknowledged that progress was poor, and he estimated that only US$10 million in external assistance should suffice to achieve eradication. A delegate of the USSR, Dr S. S. Marennikova, renewed the appeal for smallpox eradication to be given a special allocation in the budget and expressed regret that the Organization had "not availed itself of all the offers made by the Soviet Union to provide specialists—in vaccination, research, etc." In reply, Dr P. M. Kaul, an Assistant Director-General, observed that there was not so much a lack of expert knowledge "... the real difficulty was in providing sufficient vaccinators and in the organization of campaigns, an administrative point in which there was not a marked need for experts" (World Health Organization, 1962). In fact, WHO then had little notion of what was really needed, a point stressed by several delegates and reflected in the resolution adopted (WHA15.53), which called on the Director-General to compile for all countries

Plate 9.6. Marcolino G. Candau (1911–1983), the second Director-General of WHO, 1953–1973, was largely preoccupied with the difficult and costly task of the global eradication of malaria throughout his tenure. The programme, started in 1955, began to experience serious problems in the mid-1960s and was transformed into a control programme in the early 1970s. The global smallpox eradication programme began and was intensified during his period of office.

their "requirements and firm estimates of costs for their smallpox eradication programmes".

Proposed Provision of Support through the WHO Regular Budget, 1963

By the time the Sixteenth World Health Assembly was convened, in May 1963, 4 years had elapsed since WHO had committed itself to global smallpox eradication, but there was still little progress to report and little substantive information available that would permit a better estimate to be made of total needs. With prodding from Professor Zhdanov at the preceding Executive Board session, WHO made its first attempt to define which countries were endemic and which were not. The Director-General's report (World Health Organization, 1963b) concluded that there were then thought to be 44 endemic countries, of which 14 were conducting eradication programmes, 22 had programmes on paper but were not yet implementing them, and 8 had so far done nothing at all. As Professor Zhdanov pointed out, "WHO was far from having done everything possible" and urgently requested that priority should be given to the programme. "It was, perhaps, the only programme that could really be completed, and in the foreseeable future" (World Health Organization, 1963c). A summary table showing the proposed allocations for smallpox eradication was presented for the first time, but, as a delegate of the USA, Dr C. L. Williams, observed, this amounted to a mere US$227 100 for the whole of 1964. Reasoning that if only US$10 million were required in external assistance, and this over a 5-year period, he expressed the belief that funding should be provided from the regular budget so as not to have to wait for voluntary contributions. This position was supported by a number of other delegates. Dr Kaul, responding on behalf of the Director-General, argued that "the Organization was giving as much encouragement as possible; the reasons for slow progress were mainly to be found at the national level where administrative difficulties and grave material shortages had to be overcome". He added that "further [voluntary] contributions had been received recently and it was hoped that it would be possible to meet all the requirements for vaccine from that source" (World Health Organization, 1963c).

Support for a special budget, financed through assessments of Member States, was growing, but the Director-General resisted the idea. The malaria eradication programme was already recognized to be in trouble, thus endangering WHO's credibility. The provision of a special budget for smallpox eradication implied that WHO was taking primary responsibility for promoting and coordinating yet a second eradication effort. In his view, the prospects for its success were not good. It was then believed, as stated in reports prepared by WHO staff, that eradication could be achieved only if at least 80% of the population were vaccinated. From Dr Candau's own experience in working in Brazil, he knew this to be impossible in the vast Amazon region, and there were unquestionably other areas in other parts of the world in which similar difficulties would arise.

Dr Kaul's optimistic statement to the Health Assembly in 1963 regarding contributions was surprising, since, in fact, few voluntary contributions were then being received. India, at the time of the Sixteenth World Health Assembly, was desperately short of vaccine. The country had embarked

Problems of WHO Support for Smallpox Eradication in India, 1963

"At present in this Region, there are only two directly assisted smallpox projects ... Except for a nominal amount of $100, no amount is provided for supplies and equipment for the Nepal project ... [For Afghanistan] we are providing $5000 in 1963 and a sum of $12 000 for ... 1964 and 1965 for supplies and equipment. We are certainly prepared and anxious to give further assistance in smallpox eradication in our Region. However, under the existing budget provisions only marginal activities described above can be carried out.

"This brings me to the case of the Indian programme which is the largest and most important in the whole world ... In pursuance of the Assembly and Board discussions, SEARO has been promising the government in giving them every help in procuring more supplies of dry vaccine to meet their total needs for their mass programme. The government now wants to know very cogently as to how WHO is going to help them ...

"In your memorandum of 13 March you have explained to me how the Director-General's circular letter of 31 July has brought practically no response for free gifts of vaccine, vehicles and other equipment. For WHO this is a very unsatisfactory position ... One thing is certain and that is this—having once pushed a government into a vast programme of this size and a programme which has importance globally much more than nationally, any failure of this magnificent national effort would fall substantially at the door of the WHO, if not legally, at least morally."

(Extracts from a letter from the Director of the WHO Regional Office for South-East Asia to Dr P. M. Kaul, WHO Assistant Director-General, dated 4 April 1963.)

on an ambitious national mass vaccination programme, with substantial support in national currency from the USA and a bilateral gift of approximately 100 million doses of vaccine per annum from the USSR. Nevertheless, the quantity of vaccine available was far from sufficient. Indeed, shortly after the Health Assembly concluded, the Director-General made emergency appeals for vaccine for India to help to meet a projected deficit of 50–100 million doses a year. Few countries, however, had the laboratory capacity to make more than token contributions even if they were so inclined.

Voluntary Contributions

Although letters asking for contributions to the programme were sent each year by the Director-General to all countries and to UNICEF, few responded (Table 9.8). UNICEF had provided substantial support for malaria eradication and was not prepared to support another eradication programme. Mr Maurice Pate, the Executive Director, in a letter of 11 July 1962 to Dr Candau stated: "As a general policy, UNICEF has not been prepared to give assistance to a separate mass campaign for smallpox vaccination but we are quite willing to contribute to countries who wish to incorporate smallpox vaccination as a function of their public health services." As a consequence, UNICEF's contributions to the programme remained small and were intended primarily for the purchase of equipment for the production of vaccine.

Up to the end of 1963, only US$7880 in cash had been contributed to the Special Account for Smallpox Eradication and 32 million doses of freeze-dried vaccine of which 25 million came from the USSR and 2 million from the Netherlands. An additional 3 million doses of liquid vaccine were contributed by Jordan and 2 million by Mexico. Twenty-eight million doses had been distributed, but this was much less than what was needed. The problem was, in part, administrative (see Chapter 11). Samples from each lot of vaccine proposed for donation had first to be examined in a WHO reference laboratory to ensure that the lot met the requisite standards of potency and purity. Within WHO, the receipt and dispatch of samples were the duty of the unit dealing with biological standards, a small unit which was not otherwise concerned with the smallpox eradication programme. The reference laboratory, in turn, tested the specimens only when a sufficient number had accumulated to make it worth while. As a result, it was not uncommon for there to be a delay of 6–18 months between the receipt of

Table 9.8. Voluntary contributions in cash or in kind (value of vaccine donations) to the WHO Special Account for Smallpox Eradication, 1958–1966 (US$)

Country	1958	1959	1960	1961	1962	1963		1964		1965		1966		Total	
	Kind		Kind	Kind	Cash	Cash	Kind	Cash	Kind	Cash	Kind	Cash	Kind	Cash	Kind
Cyprus	0	0	0	0	0	280	0	280	0	0	0	0	0	560	0
Greece	0	0	0	0	0	0	0	0	0	4 000	0	2 000	0	6 000	0
Jordan	0	0	84 010	0	0	0	0	0	25 350	0	1 400	0	3 360	0	114 120
Kenya	0	0	0	0	0	0	0	0	0	0	0	840	0	840	0
Kuwait	0	0	0	0	2 800	2 800	0	2 800	0	2 800	0	0	0	11 200	0
Madagascar	0	0	0	0	0	0	0	0	0	0	5 102	0	0	0	5 102
Mexico	0	0	0	96 000	0	0	0	0	0	0	0	0	0	0	96 000
Monaco	0	0	0	0	0	0	0	0	0	0	0	0	306	0	306
Morocco	0	0	0	0	1 000	1 000	0	0	0	0	0	0	0	2 000	0
Nepal	0	0	0	0	0	0	0	500	0	0	0	2 564	0	3 064	0
Netherlands	0	0	20 000	0	0	0	0	0	27 778	0	616	0	3 106	0	51 500
Philippines	0	0	0	0	0	0	0	0	0	0	0	0	2 591	0	2 591
Switzerland	0	0	0	0	0	0	980	0	35 986	0	9 330	0	23 148	0	69 444
Thailand	0	0	0	0	0	0	0	0	0	0	0	0	865	0	865
Uganda	0	0	0	0	0	0	0	0	0	1 681	0	0	0	1 681	0
USSR	285 000	0	0	0	0	0	0	0	0	0	0	0	0	0	285 000
United Kingdom	0	0	0	0	0	0	0	0	224 000	0	0	0	0	0	224 000
Zaire	0	0	0	0	0	0	0	0	0	0	0	2 000	0	2 000	0
Total	285 000	0	104 010	96 000	3 800	4 080	980	3 580	313 114	8 481	16 448	7 404	33 376	27 345	848 928

Table 9.9. Status in February 1965 of vaccine contributions pledged in response to the emergency appeal of June 1963

Country[a]	Number of doses offered	Status in February 1965
Bulgaria	1 000 000	Samples awaited
Cambodia	100 000	Vaccine not satisfactory
Chile	350 000	Vaccine satisfactory; donation to be accepted on receipt of advice on value placed on it
Colombia	300 000	Results of tests awaited
France	500 000	Vaccine not satisfactory
Japan[b]	50 000	Vaccine satisfactory; donation accepted
Madagascar	250 000	Vaccine satisfactory; donation accepted
Pakistan	300 000	Results of tests awaited
Peru	3 000 000	Vaccine not satisfactory
Portugal	?	Results of tests awaited
Switzerland	2 325 000	Vaccine satisfactory; donation accepted
Tunisia	1 000 000	Results of tests awaited
United Arab Republic (Egypt)	800 000	Vaccine not satisfactory
United Kingdom	4 000 000	Vaccine satisfactory; donation accepted
Yugoslavia	1 000 000	Samples awaited

[a] Designations of countries used at the time.
[b] Although the Japanese donation was accepted, its receipt is not recorded in WHO documents; its value has therefore not been shown in Table 9.8.

samples and the notification of results. Even when the results were found to be satisfactory, further delays occurred, often of many weeks' duration, because of problems in arranging for the shipment of the vaccine. The delays in testing were sometimes so long that the production laboratory sent the lots concerned to other consumers and the whole process had to be repeated.

In response to the Director-General's emergency appeal of June 1963, a number of pledges of vaccine were made, the status of which in February 1965 (Table 9.9) illustrates some of the problems of vaccine supply at that time.

A total of 15 countries had pledged some 15 million doses of vaccine but 18 months later, as Table 9.9 shows, only about 6.6 million doses from 4 countries had been accepted, far short of the anticipated requirement of 50 million doses for India alone for 1 year.

The First WHO Expert Committee on Smallpox, 1964

Whatever the urgency conveyed in resolutions adopted by the Health Assembly, WHO took no additional measures to strengthen the smallpox eradication programme. The medical officer originally assigned to work on smallpox left the Organization in June 1963 and his responsibilities were transferred to another staff member, who dealt with smallpox only on a part-time basis.

In January 1964, WHO decided to convene an Expert Committee on Smallpox to discuss the problem. The Committee, in its report (WHO Expert Committee on Smallpox, 1964), carefully noted that the Director-General had been requested in 1959 "to prepare a programme of advice and help to countries on the basis that campaigns would be primarily the responsibility of national governments". Nothing is said in the report of the progress or lack of progress made. Although the Committee viewed the eradication of smallpox as feasible, its recommendations did not propose a substantially more responsible role for WHO, as is evident from its report:

"The success of the smallpox eradication programme within a reasonable period of time is directly linked on the one hand with the amount of practical assistance in the form of technical advice and the supply of vaccine and other essentials which the smallpox-free countries are prepared to give to the endemic countries, and on the other with the efforts which the endemic countries are prepared to put into the setting-up of effective programmes on a national or regional basis.

"The Committee's principal recommendation is that WHO should take all steps in its power to increase the international co-operation so that the success of the programme will be ensured in the shortest possible time."

The Committee's report discussed at length various aspects of the virology and immunology of smallpox and vaccinia, the steps to be taken in the conduct of a mass vaccination campaign, and other technical matters. In the execution of programmes, *preparatory*, *attack*, and *control* phases were described which resembled, in both terminology and strategy, those of malaria eradication. Following the *preparatory* phase, the entire population would be vaccinated during the *attack* phase, not unlike the corresponding phase in malaria eradication, during which all buildings were sprayed with DDT. After the completion of this phase, the *control* phase would begin, during which cases and outbreaks would be investigated and contained. The Committee placed its main emphasis on mass vaccination. It stated that vaccination of 80% or more of the estimated population had been found to be unsatisfactory in some cases and that "the target must be to cover 100% of the population". What the Committee had in mind was the situation in India, in which smallpox continued to occur in certain areas even though the number of vaccinations recorded was greater than 80% of the estimated population. The statement was made by the Committee despite the fact that assessment in India had already shown that unsuccessful vaccinations, repeat vaccinations of the same individuals and the falsification of reports on numbers of vaccinations performed meant that levels of vaccinial immunity were far lower than the reported 80% (see Chapter 15). Nevertheless, the Committee asserted that if success was to be achieved, the target must now be vaccination of the entire population. This conclusion only served to reinforce the Director-General's doubts about the feasibility of smallpox eradication.

The Committee said little about the reporting of smallpox, except to deplore its unreliability at that time and to urge that "countries in which notification of cases and deaths is defective should make an effort to effect improvements". No reference was made to the need for developing reporting systems or to surveillance and containment measures—both key factors in the post-1967 strategy.

The Seventeenth World Health Assembly, 1964

At the Seventeenth World Health Assembly (1964), Dr Kaul introduced the subject of smallpox eradication on behalf of the Director-General by stating: "The Expert Committee considered that the Organization's eradication programme had been well conceived and soundly based" (World Health Organization, 1964b), an opinion which was not expressed in the Committee's report. The principal problem, as seen by the Organization, was that of providing adequate quantities of freeze-dried vaccine. Dr Kaul pointed out that an emergency appeal for 30 million doses of vaccine, made immediately after the previous Health Assembly, had resulted in the receipt of only 7 million doses, all of which had been used.

Whatever the Expert Committee may have thought about the programme, delegates continued to express displeasure. Several pointed out that there had been no reduction in the number of reported cases between 1959 and 1963, that programmes were proceeding too slowly, and that it was time for WHO to assign priorities to its programmes and to prepare a definitive plan for the smallpox eradication programme, including provision for an adequate central and regional staff, estimates of needs and a specific time schedule (World Health Organization, 1964b). A resolution to this effect was submitted by the delegations of Australia, Chile, India, Liberia, the USSR and the USA, which, with some amendments, was adopted (resolution WHA17.43).

A Retrospective View of Progress in Smallpox Eradication, 1959–1964

Although the Director-General, in his reports to the Health Assembly, had repeatedly observed that progress was slow and unsatisfactory, the information available to WHO regarding smallpox eradication programmes and on the numbers of cases throughout the world was fragmentary at best, and little effort had been made to obtain better information. Official telegraphic reports of cases were received by WHO in conformity with the International Sanitary Regulations, and a few countries provided descriptions of the programmes which they were undertaking. Reports on national programmes varied widely in quality, from highly optimistic ones containing few data to a very small number which described in detail where, and how many, vaccinations were being performed. Notifications, as the WHO

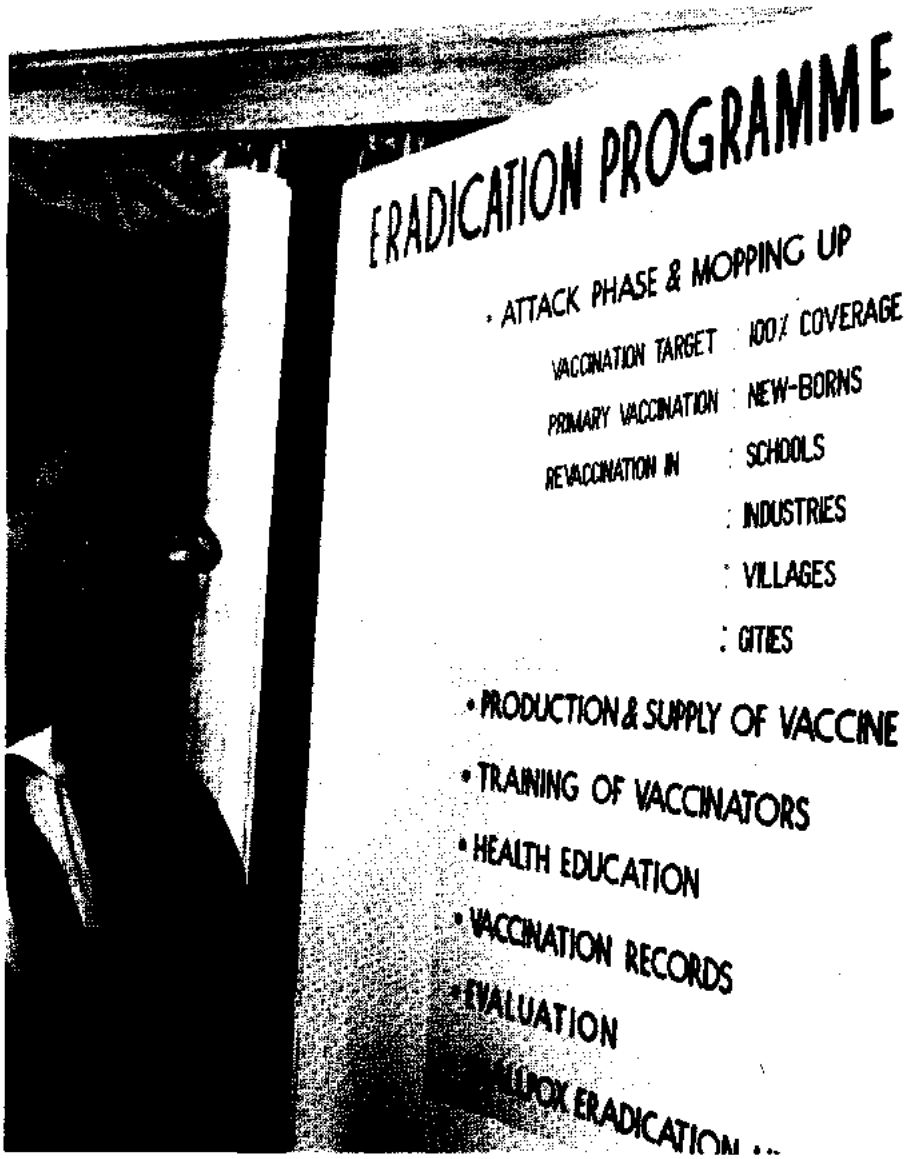


Plate 9.7. A display prepared for the WHO Regional Committee for South-East Asia in 1964. The strategy at that time focused wholly on vaccination and on achieving "100% coverage". No mention was made of the reporting of cases or the containment of outbreaks.

Expert Committee had noted, were "frequently unreliable" and "not accurate". Indeed, when reporting first began to be emphasized, WHO smallpox eradication staff estimated that not more than 5% of all cases were then being reported; later, it became apparent that the figure was closer to 1%.

Yet, more was achieved during the period 1959–1964 than was appreciated. The most significant progress was made in eastern Asia, notably the elimination of smallpox from China in 1961 or thereabouts. Had this achievement been known and properly documented, it might have provided encouragement both to WHO and to the endemic countries. The People's Republic of China, however, did not become a Member of the Organization until 1973 and provided little information about either smallpox or its programme until 5 years later. From the incomplete reports available and the observations of visitors, it was believed that China had effectively brought smallpox under control, but not until 1978, when a WHO team

visited the country, were data made available confirming that transmission had been interrupted in the early 1960s. Also, in 1959, Cambodia (Democratic Kampuchea) and Viet Nam appear to have recorded their last endemic cases although, because of the increasingly intense fighting throughout the area, their true status was also uncertain for many years. Malaysia, in 1960, and Thailand, in 1962, also succeeded in interrupting transmission following intensive, well-executed vaccination campaigns. Thus, in the period between the beginning of the global programme in 1959 and 1964, 5 large countries in eastern Asia became free of smallpox.

In western Asia also, a contiguous group of countries eliminated endemic smallpox following special vaccination campaigns conducted with varying degrees of diligence: Iraq in 1959, Democratic Yemen in 1960, Saudi Arabia in 1961, and Iran in 1963. Smallpox was, however, periodically reintroduced into these countries and others bordering the Gulf by pilgrims and migrant workers from southern Asia.

In the Americas, the regional programme of eradication begun in 1950 was continued. Although it was neither vigorously promoted nor substantially supported by WHO, Bolivia and Paraguay interrupted transmission in 1960 and Ecuador in 1963. A set-back occurred in 1963, however, when Peru was reinfected by the spread of smallpox from the Amazon region of Brazil.

Throughout much of Africa, the status of smallpox between 1959 and 1964 was less certain than in other parts of the world. Many countries were then becoming independent, civil strife was common and newly established governments were preoccupied with other matters. Health problems were but one of many concerns, and, among the specific diseases, smallpox was usually given little attention except when epidemics occurred. In northern Africa, smallpox was probably not endemic in 1959 except in Algeria, in which a protracted civil war had been in progress. Algeria's last endemic cases, however, were recorded in 1961. South of the countries bordering the Mediterranean, endemic transmission ceased or diminished to low levels in a number of the former French colonies, in which freeze-dried vaccine produced in France had been extensively employed. As became apparent during the Intensified Programme (see Chapters 17, 19 and 20), a thermostable vaccine, when reasonably widely applied in sparsely populated African countries, often served to interrupt transmission even where coverage was not uniformly high and surveillance was poor. Of the former French colonies, the Central African Republic, the Congo and Gabon appear to have become smallpox-free in 1955, 1954 and 1956, respectively; Mauritania interrupted transmission in 1962 and Senegal in 1963. The Gambia recorded its last endemic cases in 1966. In the sparsely populated countries of Djibouti and Somalia, endemic transmission ceased in 1959 and 1962 respectively, without special programmes. In Angola and the Sudan, freeze-dried vaccine was used in intensive vaccination campaigns, and those countries became free of smallpox in 1959 and 1962 respectively. However, because of the long, open borders between African countries and the generally inadequate health infrastructures, endemic smallpox recurred in Africa as a consequence of importations. Thus 3 contiguous countries—the Central African Republic, the Congo and Gabon—began again to experience epidemics of smallpox in 1961–1962, as did Lesotho, South Africa and Swaziland in 1960–1963.

Meanwhile, other countries, including Burma, Colombia, India, Pakistan and Peru, conducted major vaccination campaigns which were reported in generally optimistic terms.

When the situation is viewed in retrospect, it is evident that much was achieved by a number of countries during this period, despite the lack of external resources and despite inadequate health care structures in many of them and the use of the thermolabile liquid vaccine by most. These achievements were, however, largely unknown to WHO Headquarters staff, so that the Director-General's reports were perhaps more pessimistic than was warranted.

Events Leading to the Introduction of an Intensified Global Programme, 1965

Interest in a more important role for WHO in global smallpox eradication began to increase within the WHO Secretariat in 1964 following the appointment of Dr Karel Raška as Director of the Division of Communicable Diseases. Dr Raška, a distinguished and determined epidemiologist from Czechoslovakia, believed that smallpox eradication was an attainable objective. As he wrote: "The in-

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Plate 9.8. Karel Raška (b. 1909), a distinguished Czechoslovak epidemiologist, served as Director of the Division of Communicable Diseases in WHO Headquarters from 1963 to 1970. He was a staunch advocate within the Organization of global smallpox eradication, and played an important role in launching the Intensified Programme in 1967. He had previously been Director of the Institute of Epidemiology and Microbiology, in Prague, which contributed a number of the epidemiologists, including Ježek, who worked for the Intensified Programme.

creased expenditure on the smallpox eradication programme in developed countries would pay itself back within three years after the achievement of eradication" (Raška, 1966). Even this estimate, as it was later found, was conservative, but using this and other arguments, he was able to persuade the Director-General of the need to create a separate Smallpox Eradication unit. This was established early in 1965, although only one medical officer, Arita, and a secretary were provided to staff it.

Meanwhile, two developments in the USA provided impetus to establishing an intensified eradication programme: the development and demonstration of the jet injector for administering smallpox vaccine; and a commitment by the USA to provide technical and material support to the smallpox eradication programme. These events are summarized below and described in greater detail in Chapter 17.

Development of the jet injector

During 1964–1965, pilot field studies using the jet injector showed that it had potential in facilitating mass vaccination campaigns. The device had been developed during the 1950s for administering vaccines and other biologicals by percutaneous inoculation. A piston propelled a measured quantity of vaccine through a narrow orifice under high pressure sufficient to penetrate the skin and enter the subcutaneous tissue (Hingson et al., 1963). The fitting of a reservoir of vaccine to the injector made it possible for 500 or more vaccinations to be performed before replenishment was necessary; as many as 1000 persons per hour could be vaccinated by this means. For mass vaccination campaigns, it offered unique advantages, but before it could be used with smallpox vaccine two basic problems had to be solved: to be effective, smallpox vaccine had to be inoculated intradermally rather than subcutaneously; and the only jet injector in the 1950s which was sufficiently sturdy for large-scale use was powered by electricity and therefore unsuitable for use in the field. In 1962, Mr Aaron Ismach of the United States Army Medical Equipment Research and Development Laboratories (Millar et al., 1969) developed a special nozzle which made it possible to inoculate vaccine intradermally, and, subsequently, staff of the Communicable Disease Center (CDC) in the USA demonstrated that the technique was safe and produced as high a proportion of successful vaccinations as that obtained by conventional techniques. The problem of the power supply was also solved when Mr Ismach developed a pedal-operated, hydraulically powered model. Early in 1965, Dr Millar and his colleagues in CDC (Millar et al., 1971), serving as PAHO consultants, demonstrated in a pilot study in Brazil that a vaccination campaign using the jet injector required far less manpower than, and cost only one-third as much as, a campaign in which conventional techniques were used (see Chapters 11 and 12). Although this instrument eventually proved less useful than was initially expected, its advent stimulated the undertaking of mass vaccination campaigns.

The commitment of the USA

Further impetus was given to global smallpox eradication when, in 1965, the USA, WHO's largest contributor, began actively to support the eradication concept and in November of that year offered to provide technical and material assistance for smallpox

eradication and measles control programmes in 18 (eventually 20) contiguous western and central African countries (Gelfand & Henderson, 1966). The background to this initiative is of interest. Support by the USA for large-scale health programmes, other than those for malaria eradication and family planning, was a departure from its bilateral assistance policy at that time. The commitment to smallpox eradication emerged as a consequence of two unrelated factors: the need for a United States initiative as a demonstration of support for International Cooperation Year, a celebration of the 20th anniversary of the United Nations; and a developing regional programme, supported by the USA, for measles vaccination in western and central Africa.

United States involvement in providing measles vaccine to countries in western and central Africa began in 1961, when staff of the National Institutes of Health (Meyer et al., 1964a) demonstrated in a small study in Upper Volta (now Burkina Faso) that the new attenuated Edmonston strain of measles virus was both safe and efficacious. This was followed, at Upper Volta's request, by a country-wide measles vaccination campaign and, subsequently, by programmes supported by the United States Agency for International Development (AID) in other countries in the area (Henderson, 1967). The programme proved to be popular and, by 1965, at the request of governments in western and central Africa, AID had agreed to provide assistance to 11 of them. In the same year, CDC was approached and asked to provide the requisite technical assistance.

To Henderson, then on the staff of CDC, and his colleagues, the measles control programme made little sense, since it would inevitably be too difficult and costly for the countries concerned to sustain when bilateral assistance ceased. A regional programme for the eradication of smallpox, however, appeared to be feasible and to offer the possibility of achieving permanence. However, the control of smallpox, let alone its eradication, had not previously been considered by AID staff. Meanwhile, in a speech on 10 June 1964, the President of the United States, Lyndon Johnson, took public notice of the vaccination campaign in western Africa when he promised a new initiative in support of International Cooperation Year, stating: "I intend to dedicate this year to finding new techniques for making man's knowledge serve man's welfare ... I intend to expand our efforts to provide protection against disease." He then alluded to the measles vaccination programme in western Africa and continued: "We will expand our efforts to prevent and to control disease on every continent."

That the United States commitment might apply to smallpox did not emerge until World Health Day of the following year—7 April 1965. World Health Day, which commemorates the day the WHO Constitution entered into force in 1947, has a different theme each year. In 1965 "Smallpox Alert" had been selected as a result of many smallpox importations into Europe in 1962–1963, the intention being to stress the need for vigilance. Dr Benjamin Blood and Dr James Watt of the United States Public Health Service proposed a special presidential message for that day, committing the USA to supporting global smallpox eradication as an answer to the need for continuing vigilance against importations. Although no action was taken, a second opportunity to obtain a presidential commitment arose a month later in conjunction with the expected debate on smallpox eradication at the Eighteenth World Health Assembly. This time they were successful in persuading the staff of the President of the USA to issue a special press release: "President Johnson announced today that he has instructed the U.S. Delegation at the World Health Assembly to pledge American support for an international program to eradicate smallpox completely from the earth within the next decade." United States support was envisaged as the "contribution of technical personnel and other resources to the Pan American Health Organization ..." and "assisting in the establishment of laboratory facilities in the developing countries to help meet requirements of vaccine".

Two months after this press release, CDC proposed to AID that a regional smallpox eradication measles control programme should be established throughout western and central Africa. This was a far more extensive and costly enterprise than the more geographically limited measles vaccination campaign envisaged by AID, and quite different from the type of assistance pledged by the delegation of the USA in its statement at the World Health Assembly. The President's staff, however, on learning of the proposed plan, expressed support and, on 23 November 1965, a press release was issued which began:

"Plans for campaigns to protect 105 million people from smallpox and measles in 18 African

countries were announced today by the White House. . .AID and PHS staff are beginning consultations with African and WHO officials on plans for the campaign, its acceptability to African countries and their willingness to contribute to the program."

What had begun as a field trial of a new measles vaccine in 1961 became a smallpox eradication–measles control effort involving 20 countries of western and central Africa (see Chapter 17, Fig. 17.1); in the process, the USA formally and strongly expressed its support for the global smallpox eradication programme.

The Eighteenth World Health Assembly, 1965

At the request of the Seventeenth World Health Assembly, a comprehensive plan for a global eradication programme was presented by the Director-General at the Eighteenth World Health Assembly in May 1965 (World Health Organization, 1965b). Its preparation had been no easy task for the Secretariat, given the small number of staff assigned to smallpox eradication and the lack of information in Geneva about smallpox and smallpox eradication programmes throughout the world. To prepare the report, WHO recruited two consultants, Dr Frank Grant of Ghana and Dr P. M. Lal of India, to assist Arita. They were asked to review all available information and to visit 4 countries (Afghanistan, Burma, Mali and Nigeria) "to assess the situation and to reach some broad conclusions on the basis of a sample survey".

In his report (World Health Organization, 1965b), the Director-General expressed the belief that, so far as could be determined, 12 countries had succeeded in eradicating smallpox since 1959, but much more needed to be done. He concluded that:

(1) In many endemic countries, other health problems were considered to be of greater importance than smallpox.

(2) There was a need for, and frequent lack of, an adequate administrative and supervisory structure.

(3) Supplies of heat-stable freeze-dried vaccine in very large amounts and also transport, refrigeration and other equipment were needed, as well as short- and long-term consultants for the planning and execution of the campaigns.

(4) The maintenance phase (continuing vaccination) was as important as the attack phase if smallpox was to be prevented from recurring.

(5) Pilot projects were needed to determine strategy.

(6) Assessment of vaccination success rates by an independent team was vital.

(7) Contiguous endemic countries should start mass campaigns simultaneously.

The recommendations in the report dealt broadly with each of these points.

Introducing the report at the Health Assembly, Dr Kaul indicated that US$80 million would be needed, an estimate which was based on the assumption that the entire population of the endemic countries would need to be vaccinated, at an average cost of US$0.10 per vaccination (World Health Organization, 1965c). The estimate made no provision for the People's Republic of China, which, as previously noted, was not then a Member State of WHO. Of the total, US$28 million were thought to be required from international sources—i.e., about US$5 million a year for 6 years, rather than US$10 million, as estimated in 1963.

Dr Kaul noted that a substantial increase in effort and in material support was essential if the eradication programme was to be speeded up and achieve its goal within a reasonable time. To strengthen the argument that additional voluntary contributions should be made by the smallpox-free industrialized countries, he pointedly drew attention to the costs associated with a recent importation into Sweden.

Delegates again indicated their dissatisfaction with the slow pace of progress, but more bluntly than before. A delegate of the USSR, Dr M. A. Akhmeteli, expressed the increasing irritation of his country, declaring:

"Malaria eradication seemed to have been the favourite daughter of WHO, whereas smallpox eradication seemed to have been treated rather as a foster child. . . criticism might have been averted if concrete measures had been included in the 1966 programme . . . The delegation of the USSR would support any concrete proposal for speeding up the programme, but it wished for a real programme." (World Health Organization, 1965c.)

Sir George Godber, of the United Kingdom, echoed these thoughts:

". . . the Organization had been engaged in smallpox eradication for some seven years and . . . the programme had not met with as much success

as might have been possible. However, only WHO could get down to the root of the problem. It would be far preferable for WHO to concentrate upon smallpox eradication than to turn to some more ostentatious programme [a world health research centre then under consideration] which would lend only spurious prestige to the Organization ..."

Support for a WHO budget specifically for smallpox eradication was growing, but the USA in particular, although a promoter of smallpox eradication, was not in favour of this. Official government policy in the USA held that WHO should provide only technical assistance and advice; material support should be provided through other United Nations agencies and through bilateral and voluntary contributions to WHO. Accordingly, Dr Williams, of the United States delegation, introduced a resolution requesting the Director-General "to seek anew the necessary financial and other resources". This, of course, was what the Director-General had been asked to do by several preceding World Health Assemblies, and he had done so, but with little success. Potentially, one of the larger contributors was UNICEF, but Sir Herbert Broadley, on behalf of that organization, stated at the Health Assembly that UNICEF "would be unable to participate in a world-wide mass eradication campaign against smallpox, as it had done against malaria".

Although the resolution adopted at the Eighteenth World Health Assembly (WHA18.38) added little to what had already been said, its first operative paragraph expressed, more clearly than before, the attitude of the delegates:

> "DECLARES the world-wide eradication of smallpox to be one of the major objectives of the Organization" (World Health Organization, 1973a).

A Special Budget for Smallpox Eradication, 1966

The Director-General's position was a difficult one. If a more effective smallpox eradication programme were to be mounted, additional resources would be required, but it was apparent that voluntary contributions alone would not suffice. At the same time, malaria eradication was experiencing serious difficulties, for which additional resources were also required. However, voluntary contributions for malaria eradication had diminished markedly, thus making substantial additional funds from WHO's regular budget necessary, if only to sustain the existing level of activities. The Director-General could propose a substantial increase in the Organization's budget to meet the additional requirements of an intensified smallpox eradication programme but that was certain to be met by strong objections, especially from the industrialized countries, which provided the bulk of the Organization's funds. The Director-General's proposed budget was debated each year by the Executive Board and Health Assembly but had regularly been accepted as presented. An unacceptable increase involved the risk that the proposed budget would be rejected and that a divisive debate would follow, an outcome which had so far been avoided.

The problem was resolved by presenting a proposal in two parts. The first was the regular budget allocation, which was increased each year to permit a modest growth in WHO's activities and to compensate for inflation. The second was for a special allocation of US$2.4 million, which was identified as being explicitly for smallpox eradication; the Health Assembly could consider this separately and decide whether or not it was willing to commit these additional funds in support of the resolutions which it had adopted on smallpox eradication. If it was unwilling to do so, it would be apparent that delegates were less firmly committed to smallpox eradication than the Health Assembly's resolutions would suggest.

The allocation proposed for smallpox eradication may not now appear very large, but WHO's total budget at that time was itself not substantial. If both allocations were approved, it would mean an increase in the Organization's total budget of almost 22% and a comparable increase in the assessments of all Member States. Many countries could be expected to vote against the smallpox eradication budget: most of the industrialized countries, as a matter of policy, were opposed to substantial increases in the budgets of the United Nations specialized agencies; others, faced with difficulties in obtaining adequate amounts of convertible currencies to pay their assessments, would also object; and, finally, the smallpox-free developing countries that would not directly benefit from the programme could not be counted on for support.

Before presenting a new proposal to the Executive Board in January 1966, and then to the Nineteenth World Health Assembly in May of that year, the Director-General decided that another, more comprehensive, report should be prepared which would provide a detailed plan of action and more precise cost estimates. In September 1965, Henderson was asked by WHO to work with Arita, Dr Raška and Dr W. Charles Cockburn, chief of the Virus Diseases unit, in Geneva to prepare the document. Because accurate information on the status of programmes and the occurrence of smallpox was still largely lacking, this planning exercise was as speculative as earlier ones.

The Director-General's Report to the Nineteenth World Health Assembly

The document prepared for presentation to the Executive Board in summary form, and to the Health Assembly in full (World Health Organization, 1966b), is of interest in that it sets forth the basic framework within which the Intensified Programme began to function. Conceptually, the programme differed from that for malaria eradication in three important ways: (1) principles for programme execution were provided rather than a highly prescriptive plan, in the belief that programmes would have to differ from country to country depending on resources, local conditions and the epidemiological situation; (2) a reporting system for cases was to be developed from the inception of the programme to serve as a guide in its execution rather than introducing such a system at the conclusion of an attack phase; and (3) research was to be encouraged in the belief that, whatever might be known about smallpox, more could be discovered which would facilitate its eradication. Projections of needs and proposals for the administrative structure represented a compromise between what Henderson and Arita considered necessary and what was acceptable to the Director-General.

Strategy

A basic strategy calling for systematic vaccination campaigns employing freeze-dried vaccine was retained. A new and important additional component was surveillance—the notification and investigation of cases and their epidemiological characterization. This was an approach developed by Dr Alexander Langmuir at CDC (Langmuir, 1963), with whom Henderson had worked for the preceding decade. It had been applied in other disease control programmes in the USA, but appeared to be equally applicable to smallpox. Since this was the strategy which proved so important in the achievement of eradication, the relevant section of the Director-General's report is quoted here (World Health Organization, 1966b):

"It is necessary for the eradication programmes to develop a systematic plan for the detection of possible cases and concurrent investigation regarding the source and site of acquisition of the disease, the establishment of vaccination status and the prompt instigation of containment measures. Detailed epidemiological investigation of all cases to establish the reasons for their occurrence and the means by which they are being spread can be one of the most effective instruments to provide continuing guidance and direction in the vaccination programme. In the simplest terms, each case which occurs suggests the possibility of flaws in the programme. An outbreak, however small, demands a full critical review with appropriate revisions of the programme.

"The ultimate measure of any eradication programme is its success in reducing the number of cases to zero. So long as the disease is endemically transmitted, an eradication programme has failed to achieve its goal whatever the proportion of the population apparently successfully vaccinated.

"Even in countries with a limited local health structure, a systematic surveillance plan can and must be developed as an essential component of the eradication programme. The simplest type of approach might consist of a weekly report from each hospital and dispensary noting whether suspect cases of smallpox had or had not been seen. Simple basic information should be requested for each suspect case, consisting of name, age, sex, residence of patient and date of onset of illness. Hospitals or dispensaries failing to submit a report should be contacted promptly to ascertain specifically whether or not cases have been observed.

"This portion of the surveillance activity should be initiated concomitantly with the development of any systematic vaccination programme. Even where cases are comparatively few at the inception of the programme, detailed investigative and containment efforts should be initiated promptly. The discovery of apparent indigenous transmission should be accompanied by a two- or three-day intensive mass programme of vaccination in the

immediate area. In highly endemic countries, such detailed field appraisal may not be practical until a vaccination campaign in the immediate areas has been completed. It should not, however, be delayed until a country-wide programme has been completed...

"A regional surveillance programme is an important component part of the eradication scheme. Increasing facilities for travel plus continuing major population migrations across national borders permit ready dissemination of infection from country to country. Strengthening of the advisory staff at regional and national level to assist individual countries in the development of adequate surveillance programmes, able to render assistance promptly both in the field investigation phases and in direct containment operations and serving to integrate information obtained from the separate countries, would ensure greater success of the overall programme.

"It should be realized that the surveillance system thus being developed will be utilized not only for smallpox services but also to provide epidemiological services for other communicable diseases."

Plate 9.9. Alexander Duncan Langmuir (b. 1910), as director of the epidemiology programme at the Communicable Disease Center, Atlanta, GA, USA, from 1949 to 1970, developed the concept of surveillance and its application to the control of communicable diseases in the USA. This approach was introduced in 1967 in the Intensified Programme.

Status of smallpox

The report defined the endemic countries at the end of 1965 as including 6 in Asia (Afghanistan, Burma, India, Indonesia, Nepal and Pakistan), 3 in South America (Brazil, Colombia and Peru) and essentially all African countries south of the Sahara. The cases officially reported to WHO in 1964 numbered just under 50 000; essentially the same number was reported in 1965, and this was not significantly different in magnitude from the 60 956 cases recorded in 1960. It was pointed out, however, that little credence could be given to these figures.

From what was known in WHO, few programmes were thought to be making substantial progress. Of 8 projects which were being assisted in some manner by WHO in Africa, only those in Côte d'Ivoire and Upper Volta were doing well. Liberia and Mali, which had received more assistance, had succeeded in vaccinating less than one-fifth and one-third of their populations, respectively, in 4 years; combined yaws control and smallpox vaccination projects in Nigeria, Sierra Leone and Togo were progressing very slowly; and a project in the Sudan, begun 2 years earlier, was considered unsatisfactory. In South America, only Peru was then taking effective measures. In Asia, mass vaccination campaigns had begun in Burma, India and Pakistan, but only Burma appeared to be making satisfactory progress. WHO-assisted projects in Afghanistan and Nepal were recognized as being in serious difficulty.

Overall programme

An ambitious and, in retrospect, unduly optimistic programme was proposed which focused on the provision of support in 1967 to programmes already in operation and, in 1968, to the extension of the programmes to all other countries to be covered (Table 9.10); this made a total of 41 countries (as before, the People's Republic of China was not mentioned). The terms *preparatory*, *attack* and *maintenance* phases were used in the planning document but were later discarded when in practice they were found to be of little use. Thus, any comparison between projected and actual achievement is impossible to make.

It was expected that the programmes would differ from country to country, the vaccination campaigns in some being conducted in concert with other programmes by

Table 9.10. Planned phasing of smallpox eradication programmes assisted by WHO, 1967–1976; extracted from the Director-General's report to the Nineteenth World Health Assembly[a,b]

Country (by WHO region)[c,d]	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976
Africa, eastern[e]										
Burundi	*	**	**	**	***	***	***	***		
Kenya	*	**	**	**	***	***	***	***		
Malawi	*	**	**	**	***	***	***	***		
Rwanda	*	**	**	**	***	***	***	***		
Uganda	*	**	**	**	***	***	***	***		
United Republic of Tanzania	*	**	**	**	***	***	***	***		
Zambia	*	**	**	**	***	***	***	***		
Africa, western[f]										
Benin	**	**	**	***	***	***	***			
Cameroon	*	**	**	**	***	***	***	***		
Central African Republic	*	**	**	**	***	***	***	***		
Chad	*	**	**	**	***	***	***	***		
Congo	*	**	**	**	***	***	***	***		
Côte d'Ivoire	***	***	***	***						
Gabon	*	**	**	**	***	***	***	***		
Gambia	*	**	**	**	***	***	***	***		
Ghana	*	**	**	**	***	***	***	***		
Guinea	*	**	***	***	***	***				
Liberia	**	**	**	***	***	***	***			
Mali	**	**	***	***	***	***				
Mauritania	*	**	**	**	***	***	***	***		
Niger	*	**	**	**	***	***	***	***		
Nigeria	**	**	**	***	***	***	***			
Senegal	*	**	**	**	***	***	***	***		
Sierra Leone	**	**	**	***	***	***	***			
Togo	**	***	***	***	***					
Upper Volta	***	***	***	***						
Zaire	*	**	**	**	**	***	***	***	***	
Americas										
Argentina	**	**	***							
Bolivia	**	**	**							
Brazil	**	**	**	***	***	***	***			
Colombia	**	**	**							
Paraguay	**	**	**							
Peru	**	**	***							
South-East Asia										
Afghanistan	**	**	**	***	***	***	***			
Burma	***	***	***	***						
India	**	***	***	***	***					
Indonesia	*	**	**	**	***	***	***	***		
Nepal	**	**	**	**	***	***	***	***		
Eastern Mediterranean[g]										
Ethiopia	*	**	**	**	***	***	***	***		
Pakistan:										
East Pakistan	***	***	***	***						
West Pakistan	**	**	***	***	***	***				
Sudan	**	**	**	***	***	***				

[a] Source: World Health Organization (1966b).

[b] * = preparatory stage, or national vaccination campaign in operation; ** = attack phase; *** = maintenance phase with international assistance.

[c] Designations of countries as in 1976, except for East Pakistan, which became Bangladesh in 1971.

[d] Afghanistan formed part of the Eastern Mediterranean Region of WHO from 1969. Bangladesh formed part of the South-East Asia Region from 1972. Ethiopia formed part of the African Region from 1977.

[e] Excluding Angola, Basutoland (Lesotho), Bechuanaland (Botswana), Mozambique, Southern Rhodesia (Zimbabwe), Swaziland and South Africa. It was anticipated that eradication programmes could be carried out in these countries or territories with national financing only.

[f] Excluding Portuguese Guinea (Guinea-Bissau) and Equatorial Guinea. It was anticipated that eradication programmes could be carried out in these territories with national financing only.

[g] Smallpox vaccination campaigns were in progress in Saudi Arabia, Somalia and Yemen; however, detailed information was not available at the time the Director-General's report was prepared.

local health staff, and in others by special teams. Vaccination by means of jet injectors, supplemented by multiple-pressure vaccination, was to be used in South America and Africa, but it was felt that prior evaluation was necessary to determine whether jet injectors were suitable for use in Asia. The planning document stressed the need to ensure better vaccination coverage in the more densely populated areas and among

migrants but, wherever vaccination was performed, assessment of the results by independent teams was considered vital.

An "adequately staffed headquarters unit" of 3 medical officers was proposed, as well as the posting of a regional adviser in each of the 4 WHO regions in which endemic smallpox was present. International technical assistance personnel were expected to be required in most countries. Special emphasis was given to the need for regional staff "since the method of operations should be flexible enough to develop reasonably efficient programmes in the different epidemiological situations and health service structures in each country or area". The need for regional offices to assist in the establishment of regional surveillance systems was also noted in the document. It was proposed that funds should be provided for the development of vaccine production facilities, interregional training courses, consultants, fellowships, and necessary supplies and equipment.

Vaccine

The plan called for 220 million persons to be vaccinated in 1967 (Table 9.11). Assuming, as the report did, that the South American countries and Pakistan produced sufficient vaccine for their own needs, and that the USSR would satisfy the needs of Afghanistan, Burma and India through bilateral assistance, enough vaccine would be available for 180 million persons. Much of the rest of the deficit was expected to be met if the United States programme in western and central Africa was implemented, since that would provide some 30–40 million doses each year.

Costs

The overall cost estimates of the programme were based on crude approximations made, as before, by estimating the number to be vaccinated each year and multiplying by US$0.10. The international assistance required was assumed to be about 30% of the total, comprising the costs of external technical assistance (vaccine, transport, supplies and equipment). Overall, an expenditure of US$180 million was anticipated, of which US$48.5 million from international sources would be required (Table 9.12). The totals were substantially greater than those estimated a year before—US$80 million overall, with US$28 million from international sources. For the first year, a WHO budget of US$2.4 million was requested, or 36% of all external assistance required. The balance, it was hoped, would be made up by bilateral support or voluntary contributions. Although the estimates were rough at best and did not take inflation into account, it is worth noting that the international support ultimately provided between 1967 and 1979 (see Chapter 10, Table 10.8) amounted to approximately US$98 million, twice the projected sum.

Table 9.11. Estimated number of smallpox vaccinations to be carried out with international assistance, 1967–1976; extracted from the Director-General's report to the Nineteenth World Health Assembly

WHO Region	Estimated population, 1970 (millions)	Estimated number of vaccinations to be carried out with international assistance (millions)										
		1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	Total
Africa	190	20	60	80	60	50	50	50	30	10	0	410
Americas	160	40	60	60	30	30	30	30	0	0	0	280
South-East Asia	710	130	150	170	170	150	40	40	30	0	0	880
Eastern Mediterranean	150	30	40	40	50	20	20	10	10	0	0	220
Total	1210	220	310	350	310	250	140	130	70	10	0	1790

Source: World Health Organization (1966b).

Table 9.12. Anticipated expenditure on the Intensified Smallpox Eradication Programme, 1967–1976 (millions of US$); extracted from the Director-General's report to the Nineteenth World Health Assembly

	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	Total
Estimated expenditure	22.0	31.0	35.0	31.0	25.0	14.0	13.0	7.0	1.5	0.5	180.0
Share of international assistance	6.6	7.7	8.9	7.7	5.9	4.1	3.8	2.5	0.8	0.5	48.5

Source: World Health Organization (1966b).

Problems With the Plan

The proposed plan was the outcome of a compromise between its authors and senior WHO staff, especially in regard to financial and administrative provisions. Senior WHO staff viewed the problem as being primarily that of providing adequate resources for mass vaccination and saw little need for either technical assistance or international coordination of efforts. Henderson and Arita, believing that the programme and particularly the concept of surveillance would be difficult to implement, saw the problem differently and expressed their concern as follows in a letter of 14 October 1965 to Dr Karel Raška, Director of the Division of Communicable Diseases (each problem proved to be as great as or greater than they foresaw):

"... certain fundamental principles are key ... adequate central guidance and direction must be provided which has sufficient authority to express itself through Regional Office levels to the individually responsible countries; adequate financing is mandatory; capable staff at all levels is requisite ... The programme, as revised, has a number of inherent weaknesses in each of these major areas:

"(1) *Central staff*—The proposed staff both at headquarters and at regional levels is ... far less than adequate to undertake the job ... the general scheme of the proposed programme is different from programmes of the past; surveillance techniques and their application are unknown in every one of the countries ... a substantial amount of training, guidance and assistance will be required from well-trained full-time staff within the Organization ... The relationship of the Regional Offices to the programme, central headquarters and country programmes should be carefully examined. Already we sense potential conflicts in policy with AMRO [Regional Office for the Americas], AFRO [Regional Office for Africa] and SEARO [Regional Office for South-East Asia].

"(2) *Financing*—More than half of the anticipated external budget for supplies and equipment must be forthcoming on some sort of volunteer basis from other international organizations or bilateral assistance programmes ... Voluntary contributions, however ... have been negligible ... In the light of recent past experience, we question whether this is sound ... we are still concerned that a maximum of flexibility in application of funds be maintained both within Regions and between Regions and between budget categories.

"(3) *Staff*—We gather there are major difficulties at this time in recruitment of competent staff ... The necessity of the headquarters and regional WHO smallpox staffs undertaking some responsibility in this regard should be recognized and central staff augmented accordingly ... Realistically, we suspect that the programme will be obliged to rely principally on comparatively junior medical officers who can be given intensive training and carefully supervised in their field work ... However, intermediate and senior level supervisory people would be requisite. They are not provided for under the revised proposal."

Research

A statement that there was a need for continuing research on the epidemiology and virology of smallpox was inserted despite the objections of senior WHO staff, who believed, as they had with malaria, that enough was known about smallpox and that the only problems were the mobilization of resources and administration. To obtain agreement to include a section on research, a sentence had to be added: "It is hoped that total or partial financial support for many of these [research] projects will be provided directly to the responsible investigators from national funds."

The Discussions at the Executive Board (January 1966) and at the Nineteenth World Health Assembly (May 1966)

Dr Kaul introduced the Director-General's report at the Executive Board session in January 1966 and Mr Siegel described the

implications of a second appropriation for smallpox eradication. Dr Kaul noted that the Director-General, in his regular budget, had foreseen the need "to provide the impetus, direction, coordination and supervision on a global basis" and, accordingly, had proposed for 1967 the provision of US$200 000 in the regular budget (World Health Organization, 1966a). This included both funds administered by WHO on behalf of the United Nations Expanded Programme of Technical Assistance and PAHO funds. Attention was not drawn to the fact that the amount proposed for smallpox eradication was actually the smallest since 1963. Mr Siegel introduced the special appropriation for smallpox eradication. WHO's effective working budget for 1966 had been US$42 442 000; the corresponding figure proposed for 1967 was US$47 242 000, an increase of 11.3% (World Health Organization, 1965d). Two possible figures for the appropriation for smallpox eradication were offered: US$1 million and US$2 415 000. If US$1 million extra were provided for smallpox, the increase in the overall budget would be 13.7%; if US$2 415 000 were provided, it would be 17.0%. Tables had been prepared showing the additional assessments for each country for additions to the regular budget of US$1 million and US$2 415 000. If US$2 415 000 were provided, the additional cost for the smallpox programme for the USA, for example, would be US$801 660; for Czechoslovakia, US$25 440; and for the United Kingdom, US$165 210. For purposes of comparison, the estimated annual costs of routine national vaccination activities, as determined at that time by those countries were: USA, US$20 million (later studies revealed the amount to be almost US$150 million), Czechoslovakia, US$1 million, and the United Kingdom, US$650 000. In the course of the debate, however, the fact was noted that the United Kingdom had spent US$3.8 million to control imported outbreaks in 1962–1963.

After prolonged discussion the Executive Board agreed, in principle, to recommend to the Health Assembly the creation of a special appropriation for smallpox eradication in the regular budget, although most Board members expressed the belief that the amount allocated for smallpox eradication should probably be no more than US$1 million, at least for the first year.

At the Nineteenth World Health Assembly (May 1966), the Director-General's report on smallpox was presented to one of its two principal working committees, the Committee on Programme and Budget. There was, however, only a brief discussion before the Committee was required to resume a suspended debate on a draft resolution on malaria eradication, a resolution which deplored its slow rate of progress and actual regression in several countries. Before the debate could be resumed, the Committee took up the question of the overall WHO budget for 1967, the principal point at issue being the amount, if any, to be added for smallpox eradication.

The total budget figure under consideration by the Health Assembly, including funds for smallpox eradication, was US$51 515 000, an increase, the Director-General said, of 15.8% over the corresponding level for 1966, including the supplementary estimates for that year (World Health Organization, 1966c). For purposes of comparison, it is useful to note what the assessments of certain countries would have been for a budget of this magnitude. The Financial Report for 1967 shows that in that year only 5 countries contributed 5% or more of the budget—USA, US$16.6 million; USSR, US$7.1 million; Federal Republic of Germany, US$3.5 million; United Kingdom, US$3.4 million; and France, US$2.9 million—while 52 countries contributed the minimum amount, which that year was US$21 320 (World Health Organization, 1968).

The developing countries, the principal recipients of the Organization's funds, usually argued for large increases in the budget; especially strong support for the smallpox eradication programme was voiced by delegates from the countries of western and central Africa, which had been promised assistance by the USA for a regional smallpox eradication–measles control programme. However, Professor E. J. Aujaleu, an eminent French government official and for many years a delegate of France, expressed a view frequently taken by delegates from most of the industrialized countries—namely, that the Organization's budget should not, in principle, increase faster than the average annual increase in the gross national product of its major contributors. He suggested that an overall increase in the budget of between 5% and 6% would have been more appropriate; other delegates proposed figures ranging from 4% to 8%. He and other delegates also suggested that the smallpox eradication pro-

Table 9.13. Nineteenth World Health Assembly, May 1966: results of votes on budget proposals

Proposed by:	Working budget proposed (US$)	Members present and voting	Number needed for two-thirds majority	Result of vote		
				For	Against	Abstentions
France	50 000 000	84	56	18	66	17
USA	50 415 000	90	60	36	54	7
Director-General	51 515 000	86	58	60	26	12

Source: World Health Organization (1966c).

gramme might have an opportunity to become better established if a more modest beginning were to be made in 1967 and the programme expanded later. He proposed an overall budgetary ceiling of US$50 million, with approximately US$1 million earmarked for smallpox eradication. This proposal was supported by Canada, Italy, Turkey and the USSR. A compromise proposal was put forward by the USA, providing for a budgetary ceiling of US$50.4 million, of which US$1.4 million would be set aside for smallpox eradication. This proposal was supported by Australia, Austria, Belgium, the Federal Republic of Germany, Iraq, Japan, the Netherlands and Pakistan. Yugoslavia endorsed the United States proposal for a budgetary ceiling, provided that the full amount of US$2 415 000 was allocated to smallpox eradication. Meanwhile, several countries indicated simply that they could not agree to the budget as proposed (Argentina, Czechoslovakia, Hungary, Poland, Romania and Venezuela); 19 developing countries, plus Finland, Norway, Sweden and Switzerland, spoke in favour of the Director-General's budget proposal. At the closure of the debate, successive votes were taken on the proposals advanced by France and the USA (Table 9.13), a two-thirds majority of Members present and voting being required for approval of the budget.

The proposals put forward by France and the USA were defeated, and a larger budget, providing all the requested funds for smallpox eradication, was accepted by a margin of 2 votes—the narrowest margin for the acceptance of a budget in the Organization's history. In perspective, the sum appropriated for smallpox eradication was not large, considering that programmes were expected to be conducted in 41 countries, thus providing an average allocation of less than US$60 000 per country per year. However, the total sum accounted for 4.7% of WHO's total budget and was some 10 times greater than the sum allocated in the Organization's 1966 budget.

When the Committee on Programme and Budget resumed discussion of the proposed smallpox eradication programme, whose budget was now assured, delegates expressed their general support. In the course of the debate, Dr D. Venediktov, a delegate of the USSR, announced that his country would make a contribution of 25 million doses of vaccine each year for 3 years, a contribution which the USSR continued annually throughout the global programme; Dr Blood, a delegate of the USA, briefly described the commitment of the USA to programmes in western and central Africa; and additional assistance was promised by the League of Red Cross and Red Crescent Societies. The Director-General was requested to seek help from the World Food Programme, UNICEF and UNDP, as well as bilateral agencies. Although bilateral support was to play an important contributory role, relatively little assistance from other international organizations ever materialized.

The programme was thus accepted by the Health Assembly, albeit with less than unanimous conviction and commitment. Privately, many delegates were sceptical about the prospects for global eradication, although all were basically in agreement that better smallpox control would benefit both the countries in which smallpox was endemic and those subject to importations of the disease.

Preparations for Initiating the Intensified Programme, 1966

By January 1966, when the Executive Board decided to recommend a special allocation for an intensified smallpox eradication programme, the global programme had been in progress for more than 6 years, but few WHO personnel had been assigned to it. The smallpox eradication staff consisted of a medical officer and a secretary in Geneva; 2 recently assigned African intercountry advisers, in Kenya and in Liberia; and 3 advisers assigned at country level, in Afghanistan,

Bolivia and Mali. With little known about the status of smallpox in the endemic countries or their prospective programmes or needs, major efforts were required to mount a fully fledged global programme capable of effectively utilizing the US$2 415 000 provided in the budget.

In February 1966, immediately after the Executive Board session, the Director-General sent letters to each of the WHO regions indicating the possibility that additional funds specifically for smallpox eradication might be made available. Each region was requested to develop provisional plans for 1967–1968, based on a larger budget, and to identify their needs for vaccine, advisory personnel, supplies and equipment. In the Americas, a regional adviser was appointed, who immediately began discussions with the authorities in Brazil as well as with those of Argentina, Colombia, Ecuador and Peru, in which it was thought that programmes would be required.

Meanwhile, at CDC, Henderson was assembling staff, procuring equipment and working out plans with 16 countries of western and central Africa so as to permit programmes to begin there in January 1967 (see Chapter 17).

Late in May 1966, with the Health Assembly's formal approval of the programme and budget, activities steadily increased. Henderson was recruited to serve as chief of the Smallpox Eradication unit, a post he was to assume in November; a second medical officer, Dr Stephen Falkland, was temporarily assigned through transfer from another unit in WHO, and an administrative officer was assigned from the malaria programme. One or two consultants were recruited to visit countries in each of the 4 WHO regions in which smallpox was present to encourage them to develop national programmes.

Within the Organization, however, reservations about the wisdom of smallpox eradication were widespread and were reflected in administrative actions. The Director-General, in a meeting with regional directors immediately after the Health Assembly, privately expressed his doubts about the feasibility of eradication and cautioned them about imposing on countries a special programme like that for malaria eradication. As he saw the situation, the prospects for success depended on progress in the development of each country's basic health services. It was not surprising, therefore, that a memorandum, dated 10 August 1966, was sent to all regional offices by two Assistant Directors-General, Dr Kaul and Dr John Karefa-Smart, which stated:

> "The establishment of permanent basic health services should be given the highest priority since it is a prerequisite for the success of the smallpox eradication programme in any area and you should be prepared to consider providing from the smallpox eradication programme resources, such assistance as may be required for developing and strengthening basic health services in the area where the campaign is launched."

This policy statement effectively authorized the use of smallpox eradication funds to meet almost any of the all but inexhaustible needs of the basic health services.

In conformity with their belief that the smallpox eradication programme called for little more than the proper distribution of resources, senior WHO staff in July 1966 substantially reduced the Headquarters smallpox eradication budget. Funds for staff travel were reduced from US$6400 to US$2400, then sufficient to permit a total of approximately 3 trips of 21 days each; funds for consultants were cut so as to allow for only 3 man-months instead of 23; and funds for convening a meeting of a scientific group were cancelled. The research budget was reduced from US$30 000 to US$12 000 and responsibility for administering these funds was assigned to the Virus Diseases unit. Dr Raška vigorously objected to the changes and argued that travel funds should be increased to US$14 000 and that a medical officer and 2 secretaries should be added to the personnel complement to create a unit staff of 7 (3 medical officers, an administrative officer, a technical assistant and 2 secretaries). The funds were eventually restored and the increase in personnel was approved when, in a meeting with the Director-General, Dr Kaul and Dr Raška, Henderson expressed doubt that he could manage a global programme of such magnitude without the resources stipulated and proposed to withdraw his candidature for the post of unit chief. Although that possibility was considered, Dr Raška eventually prevailed.

CDC staff, meanwhile, were working intensively to launch the AID-supported programme in western and central Africa. By the end of 1966, agreements had been signed with most of the countries concerned, a staff of 50 had been recruited and trained, operations

manuals had been prepared, and supplies and equipment had been procured. The CDC training programme concluded with an address, given by special invitation, by the Director-General of WHO and delivered by telephone on 31 August. His comments are noteworthy for two points. First, he stressed his concern that another special programme like that for malaria eradication might be developed: "You must jointly ensure that the smallpox eradication programme is a coordinated effort within the general health services of the country, and not a separate, isolated activity." Secondly, he stated: "The programme of eradication is planned over a period of 10 years", a goal which had been mentioned in the Health Assembly although not stated in the formal resolution. Uncertainty about the eventual outcome of the programme, however, subsequently led to instructions to omit any reference in official documents to the 10-year target date.

The attitudes of the WHO regional directors ranged from the interested, in the Americas (Dr A. Horwitz) and Eastern Mediterranean (Dr A. H. Taba), to the reluctant in the African Region, and to the frankly negative in the South-East Asia Region. In a letter to Dr Kaul (19 July 1966), the Director of the Regional Office for South-East Asia wrote: "In our view, on account of the organizational and administrative weakness of health services and serious socio-economic as well as financial difficulties, smallpox eradication is not likely to be achieved in the countries of this Region in the near future."

A programme which was rudimentary at best at the beginning of 1966 saw a quantum change in the level of activity by the end of the year. Henderson, Arita and Dr Falkland in the Headquarters unit were joined by Dr G. P. Nikolaevskij, a physician from the USSR, and Mr John Copland from the USA, who was to serve as the unit's administrative officer over the succeeding decade. Programmes in 16 countries of western Africa were about to commence; plans of operations had been signed with Brazil and the Democratic Republic of the Congo (Zaire); Dr Ehsan Shafa had been appointed Regional Adviser on Smallpox Eradication for the Eastern Mediterranean Region, and Dr Bichat Rodrigues in the same capacity for the Americas; and discussions had begun with a number of countries in the Eastern Mediterranean and South-East Asia Regions regarding eradication programmes.

Voluntary contributions to the programme during 1966 continued to reflect the general lack of interest among donors. Apart from vaccine donated by Switzerland, contributions in cash and in kind from Greece, Jordan, Kenya, Monaco, Nepal, the Netherlands, the Philippines, Thailand and Zaire were valued at only US$17 632.

As the Intensified Programme commenced operations, however, the areas with endemic smallpox were actually substantially smaller than they had been in 1959 (see Table 9.6). The information now available indicates that in only 31 countries or territories, with a total population of 1 078 775 000, was smallpox endemic in early 1967, compared with 59 in 1959. Nevertheless, the problem remained formidable.

SUMMARY

Since smallpox was such a good candidate for global eradication, it is surprising that the commitment to undertake such a programme was so long delayed and, even after being accepted by the World Health Assembly, so ill-supported both within WHO and by most Member States. In part, this derives from the historical roots of human disease eradication programmes originating, as they did, in vector control programmes, which continued and eventually culminated, in 1955, in the vast and costly global effort to eradicate malaria. Many of the leading figures in international public health during the 1960s had spent their formative years in vector control programmes, and it was with these that they were the most conversant and felt the most comfortable. Among the most important of the experts concerned were clearly Dr Soper, Director of the Pan American Sanitary Bureau for 12 years, and Dr Candau, Director-General of WHO for 20 years. Reluctance to undertake global smallpox eradication may also have originated, in part, from concern about the chances of such a programme being successful in Africa, where, in most areas, the transport, communications and health services infrastructures were poorly developed. Although malaria eradication had been undertaken with alacrity in 1955, and had been referred to as "global" in scope, Africa south of the Sahara had not been included in the programme. Perhaps of equal importance was an unstated acceptance of smallpox as an inevitable, entrenched disease

for which vaccination, a permanent feature of public health practice for more than a century, would always be required. Such, at least, was found to be the widely held belief, even after global eradication had been achieved and documented.

The first to call for regional smallpox eradication was the Pan American Sanitary Organization in 1950, and although its programme was reasonably successful as far as it went, it was not actively promoted or diligently pursued. In part, this reflected Dr Soper's preoccupation with eradication of the *Aedes aegypti* mosquito and, later, with malaria eradication. The lack of vigour can also be attributed to the fact that the largest endemic country was Brazil, in which the prevailing mild variola minor was not an important public health problem.

The proposal by the USSR in 1958 that a global programme to eradicate smallpox should be undertaken represented a new departure rather than, as some have believed, a logical extension of the regional programme in the Americas. Professor Zhdanov, the author of the proposal, reasoned correctly that smallpox eradication was a far more attainable objective than the eradication of malaria and that such a programme would benefit all countries, including his own, which shared a long border with endemic Asian countries.

Between 1959 and 1966, lack of interest on the part of WHO in smallpox eradication and the perceived lack of progress in the programme must be attributed, in large measure, to WHO's preoccupation, as well as that of many Member States, with malaria eradication. Over this period, the persistent advocacy of smallpox eradication by the USSR in the World Health Assembly served to sustain interest in such a programme on the part of Member States, even though the Organization assigned few resources to it. Renewed interest in the programme was stimulated by the commitment of the USA in 1965 to support regional smallpox eradication programmes in a contiguous group of countries in western and central Africa, a decision which was less a product of rational policy analysis than a reluctantly accepted by-product of a regional measles vaccination campaign.

The decision by the World Health Assembly in 1966 to intensify the effort to eradicate smallpox was made with grave reservations. Eradication, as a concept in disease control, had largely been discredited, and the Director-General himself, believing smallpox eradication to be an unachievable objective, viewed the programme as one which could serve only further to undermine the Organization's credibility. Potential contributors to WHO's voluntary fund were demonstrably no more enthusiastic, and UNICEF, discouraged by the failure of the costly malaria eradication campaign, refused to support the programme as a matter of policy.

The Intensified Smallpox Eradication Programme was thus conceived in an atmosphere of sanguine rhetoric overshadowed by real doubts abouts its ultimate success.

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CHAPTER 10

THE INTENSIFIED SMALLPOX ERADICATION PROGRAMME, 1967–1980

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INTRODUCTION

The prevention and ultimately the eradication of smallpox constituted, in principle, one of the simplest and most straightforward of disease control activities. Effective long-term protection was provided by the single application of a vaccine which was easy to administer and highly stable even under tropical conditions. The presence of smallpox in an area could be readily detected because of the characteristic rash it produced, a rash which was readily identifiable by programme staff and villagers alike. Only patients with rash transmitted the infection to others, and then only to persons with whom they were in close contact. Because 10–14 days elapsed between each generation of cases, smallpox usually did not spread rapidly and epidemics took time to develop. Little more was required to control its spread than the isolation of the patient and the vaccination of his close contacts.

Despite the simplicity of both smallpox control and the strategy for its eradication, implementation of practical field programmes over a finite time span and on a global scale was a complex and difficult task. The achievement of eradication and its certification ultimately required the cooperation of all countries. The participation of an international agency—the World Health Organization—was important, and probably essential, in ensuring such cooperation. As the international organization with technical responsibility for health programmes, WHO was requested by resolution WHA20.15 of the Twentieth World Health Assembly "to elaborate and implement the detailed plan, including the co-ordination of all international, bilateral and national efforts" for the Intensified Smallpox Eradication Programme (World Health Organization, 1973a). In carrying this out, however, WHO had no authority, other than that of moral suasion, to compel any country to initiate a programme, adhere to a plan or strategy, or contribute towards its support. For this reason, the global programme had to evolve within a framework of broad principles and expectations, pragmatically modified by reality, rather than within the confines of a comprehensive master plan having specific and enforceable time-limited goals.

In November 1967 the entire professional and secretarial staff of WHO throughout the world (including short-term consultants and

WHO agents in Zaire) numbered only 3302 persons, few indeed to cope with the array of tasks and responsibilities with which the Organization had been charged by the World Health Assembly, its governing body. Those assigned to smallpox eradication were likewise few in number, the staff of professional grade in no year comprising more than 150 persons (including consultants), of whom no more than 6 were in Headquarters and, at most, 7 in the WHO regional offices. They were expected to promote special programmes in more than 50 countries and to guide and coordinate activities which, at times, involved as many as 150 000 workers.

The programme presented unusual challenges for WHO, because the administrative structure and procedures of the Organization were primarily designed for the purpose of providing technical assistance, rather than material support, to a wide range of health projects in many different countries, few of which needed to be coordinated with others. Smallpox eradication, in contrast, required the provision of substantial material support and far closer collaboration among countries and among largely independent WHO regional offices, both in programme execution and in resource allocation.

The Director-General, Dr Marcolino Candau, had foreseen the need to mobilize substantial voluntary contributions in support of the programme but, in 1967, the Organization had had only limited experience and little success in obtaining contributions of this type. Significant donations for smallpox eradication—apart from some bilateral contributions—did not begin to be received by WHO until more than 7 years had elapsed. The consequent lack of resources constituted a serious, continuing problem and, even in the concluding years of the programme, those that were made available barely sufficed to sustain momentum. Donated vaccine, for example, was continually in short supply despite repeated appeals for assistance. The World Health Assembly was informed on a number of occasions of the need for additional funds, amounting to no more than a few million US dollars, and such funds were sought in correspondence and in meetings with potential donors, but the response was never adequate. Expenditures for smallpox eradication from WHO's own regular budget, measured in constant dollars, seldom exceeded US$2.4 million annually, the amount initially appropriated by the Nineteenth World Health Assembly in 1966. Thus, restraint and compromise in field operations were necessary even when global eradication appeared imminent. Success was never a certainty even during the years immediately preceding the last known cases.

The problems of sustaining international commitment and support were formidable but no less so than those in many of the countries with endemic smallpox. Successful national programmes required a political commitment to undertake eradication, but smallpox was not a concern of high priority for some countries, even though they might have voted for World Health Assembly resolutions in favour of its eradication. Sustaining a commitment to the programme was no less difficult because, in many countries, governments changed frequently, as did the responsible health officials, and such changes led to the readjustment of national priorities. Famine, flood, epidemic cholera and the like often diverted smallpox eradication programme resources for long periods; civil war in Ethiopia, Nigeria, Pakistan and Uganda caused serious disruptions in operations; and collaboration with several governments in southern Africa, as well as some in Asia, was all but impossible owing to political constraints.

After smallpox had been eradicated, however, many persons inside and outside WHO mistakenly concluded that the achievement could be attributed to a generously financed, enthusiastically supported and authoritatively directed programme similar to a military campaign. That the programme had none of these characteristics is apparent from this and the succeeding chapters.

This chapter describes the context within which the programme functioned in WHO and how the overall campaign developed and matured, how national programmes were established, how international coordination was achieved, how personnel were recruited and budgetary problems resolved, how supplies of vaccine were obtained and handled, and how research contributed to the effort. All these activities were interrelated, and critical constraints or important developments in one area affected progress in others. For clarity of presentation, different elements of the Intensified Programme are discussed individually, beginning with the overall strategic plan and the programme's administrative structure, relationships and personnel at the international level. This is followed by a

description of the way in which national governments became committed to the programme. A discussion of resources, surveillance and research, from an international perspective, is followed by a general description of the approaches adopted and results obtained in national programmes of vaccination and surveillance. To provide an overall perspective and an introduction to the chapters describing national programmes (Chapters 12–23) and certification activities (Chapters 24–27), a brief chronological summary of events concludes the chapter.

THE STRATEGIC PLAN

As described in the Director-General's report on smallpox eradication to the Nineteenth World Health Assembly (World Health Organization, 1966b), the strategic plan for eradication during the Intensified Programme was 2-pronged: (1) mass vaccination campaigns in which freeze-dried vaccine of assured quality was employed and which were assessed by special teams, and (2) the development of a surveillance system for the detection and investigation of cases and the containment of outbreaks. In the execution of the programme, 3 principles were considered to be of special importance: (1) all countries would need to participate and their efforts would require regional and global coordination; (2) flexibility and adaptability would be required in the implementation of national programmes; and (3) ongoing research, both in the field and in the laboratory, would be needed to evaluate progress, define alternative directions and methods, and solve problems as they arose.

To foster a common understanding of principles and procedures among a geographically far-flung programme staff, a comprehensive mimeographed manual entitled *Handbook for Smallpox Eradication Programmes in Endemic Areas*, hereafter referred to as the WHO Handbook, was issued by the Organization in July 1967 (SE/67.5 Rev. 1, World Health Organization). It was an elaboration and adaptation of a manual developed in 1966 for the programme supported by the USA in western and central Africa (see Chapter 17). The foreword to the WHO Handbook encouraged programme staff to innovate and to adapt as needed, since programmes should evolve and change with experience. For this reason, the WHO Handbook was deliberately referred to as a "draft", in the expectation that revised versions would be prepared in subsequent years on the basis of field experience. Because of the small number of staff available in Geneva and the speed with which the programme developed, no revised version was ever issued, other means being used for passing on from one country to another new and important observations and approaches. The WHO Handbook included a wide variety of information, ranging from an account of the clinical features of smallpox and the methods used in laboratory diagnosis to a description of operational approaches for vaccination campaigns and surveillance programmes; it also described methods for use in health education, and the management of administrative and transport services. The Handbook concluded with a section describing more than 20 subjects of interest for field and laboratory research.

The basic strategy, with certain modifications in emphasis and subsequent elaboration of methods for its implementation, withstood the test of field experience. Vaccination campaigns, however conducted, were expected to reach at least 80% of the population in all areas, and higher, but unspecified, rates of coverage in the more densely populated cities and towns. The figure of 80% was not based on any epidemiological criterion, but represented what was believed to be an achievable goal in a well-conducted programme. As an indicator of the use of potent vaccine, the plan called for a take rate of at least 95% for primary vaccinations. To determine whether these objectives were being met in a given area, independent assessment teams were expected to monitor the results in a sample of the population soon after the campaign had concluded in that area.

Although assessments of coverage and take rates were considered to be important quality control measures in the vaccination campaigns, the WHO Handbook emphasized that "the success of the programme, therefore, is appraised ultimately by the occurrence or absence of endemic smallpox and the *principal assessment technique, accordingly, is surveillance*". Surveillance was to be based on a reporting system in which all existing medical and health units participated. This was to be supplemented by the immediate investigation of reported cases and a critical review of outbreaks to determine how and why small-

pox was being spread. The WHO Handbook stated that:

"... surveillance thus is an essential component of the programme since the term 'eradication' implies that the number of indigenous cases of smallpox is '0'. However extensive a country's vaccination campaign, however accurately assessed, a country with an inadequate system for surveillance cannot determine whether ... eradication has been achieved."

Since it was recognized that surveillance was a new concept and might be difficult to implement in highly endemic countries, a phased programme for its development was proposed (see Chapter 17, Table 17.4).

Mass vaccination was a familiar and readily acceptable concept to public health officials. Assessment of the quality of work and of progress, on the other hand, had not been common practice. Few were accustomed to measuring the success of their efforts and many, in fact, had never questioned whether the vaccine in use was satisfactory or had been properly stored. Both assessment and surveillance proved difficult to incorporate into most programmes.

THE WORLD HEALTH ORGANIZATION

Among the international agencies, WHO has played a pre-eminent role and acquired substantial experience in providing technical assistance and cooperation for health programmes and in the development of international health policies. Other international agencies—e.g., UNICEF and the United Nations Development Programme—have provided substantial material assistance for health programmes, but WHO, from the time of its foundation, has seen its main task as that of providing technical guidance (Finkle & Crane, 1976). WHO, like all large administrations, has gradually evolved its own patterns and traditions of management and, while a full exposition of this subject is beyond the scope of this book, certain features are important to an understanding of the course of development of the global smallpox eradication programme.

In a comparative analysis of 8 major international organizations, Jacobson (1973) characterized the role of the Director-General of WHO as being unusually significant and influential. He described the Organization as a "strong and stable system", but noted that it was "dominated by the ideology of medicine" and "by a strong commitment to regionally decentralized service activities". Because of this decentralization of activities and responsibility within WHO, its regional directors have also played unusually important roles. They and the Director-General are the only elected officials of the Organization. If after a term of office of 4–5 years they wish to be reappointed, they must stand for re-election by Member States. The factor of re-election inevitably has a bearing on their decisions regarding the recommendation of projects, budgetary allocations to countries, appointment of staff by nationality, and other matters. Continuity of the elected leadership, however, has been the norm. Although the first Director-General, Dr Brock Chisholm, served for only 5 years (1948–1953), his successor, Dr Marcolino Candau, served for 20 years (1953–1973), and Dr Halfdan Mahler has held the office since that time. For most regional directors, a long term of office has likewise been the norm.

The Members and Governing Bodies of WHO

The World Health Assembly, which decides WHO's policies and programmes, consists of delegates representing Member States, each Member State having one vote. It normally meets once a year, usually in May. Guidance to the Health Assembly is provided by the Executive Board, a smaller body, whose members serve in a personal rather than an official capacity but are designated by the governments of Member States elected by the Health Assembly. The Board meets twice a year, the main meeting being held in January, while a second, shorter, meeting takes place immediately after the Health Assembly.

The Twelfth World Health Assembly (1959) and the Nineteenth World Health Assembly (1966) committed WHO to the global eradication of smallpox although some countries were not then Members of the Organization and hence not party to these decisions. Among those which, in 1966, were not yet Members or were not yet directly represented were the People's Republic of China, the German Democratic Republic, the Democratic People's Republic of Korea and the Socialist Republic of Viet Nam. Until the 1970s, no official communication between

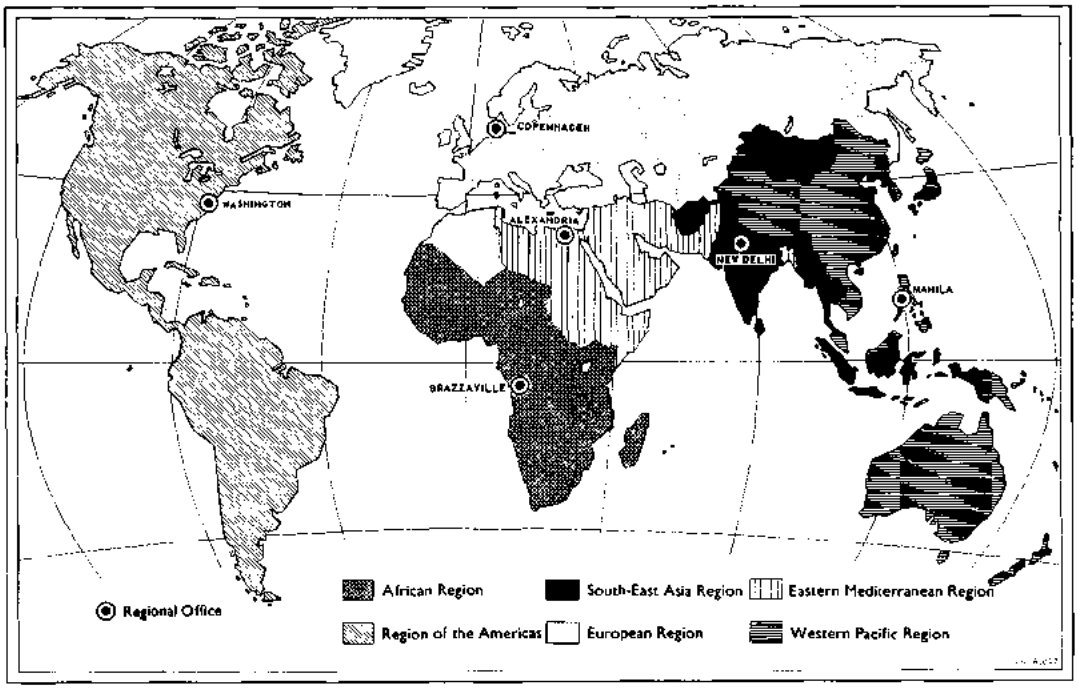


Fig. 10.1. WHO regional offices and the areas they served, December 1967. Whereas there were 167 Member States and Associate Members of WHO in December 1986, there were only 129 when this map was prepared (from World Health Organization, 1968a). A number of countries or territories shown here as served by WHO regional offices were not directly represented in WHO in 1967, the largest among them being the People's Republic of China

WHO and these governments was possible and little official information was available from some of them about the status of smallpox in their countries. None was thought to have endemic smallpox in 1966, although it was not possible to confirm this until after they became Member States of the Organization. Besides these countries, there were 4 other large territories, all in Africa, which in 1966 either no longer participated in WHO (South Africa) or were represented by colonial powers (Angola, Mozambique, and Southern Rhodesia). All except Angola had endemic smallpox in 1967. Until the 1970s, however, it was difficult or impossible for WHO to communicate with these countries as well, either about the occurrence of smallpox or about the status of their programmes. Thus, effective universal participation in the smallpox eradication programme was not achieved until a number of years after the Intensified Programme had begun, and not until 1979 were communications adequate with all countries so that global eradication could be certified.

Each Member State is attached to one of WHO's 6 regions (Fig. 10.1), only 4 of which had endemic smallpox in 1967—Africa, the Americas, South-East Asia and the Eastern Mediterranean. Regional committees, at which Member States of the respective regions are represented, meet once a year to decide regional policy and to examine the regional director's proposed programme budget for transmission to the Director-General and inclusion in the Organization's global programme budget.

The type of representatives sent by Member States to the Health Assembly and the regional committees had a bearing on the smallpox eradication programme and on the outcome of resolutions. An analysis of delegates to the Twentieth World Health Assembly (1967) showed that 80% were representatives of health ministries (Jacobson, 1973); while that was logical and often advantageous, it was sometimes a handicap to obtaining voluntary contributions from governments and to securing national commitment to undertake eradication programmes. Volun-

tary contributions from the industrialized countries were usually provided by a development agency separate from the ministry of health and, as experience showed, liaison between the two was frequently deficient. Programme policies and needs identified by the World Health Assembly were often not understood by the development agencies and sometimes, because of this, appeals for voluntary contributions went unheeded. The way that the countries with endemic smallpox were represented also gave rise to problems. Ministries of health, to which most delegates belonged, were often politically weak, the minister often not being of cabinet rank. Decisions with regard to the allocation of national resources were often made elsewhere in government—e.g., in planning departments, few of whose members attended the World Health Assembly. Thus, the commitment of some Health Assembly delegates to undertake national programmes meant little from the point of view of their implementation.

Role of the Director-General

Decisions on policy and budgetary allocations were ultimately the responsibility of the Health Assembly, acting on the advice of the Executive Board but, as Jacobson (1973) points out:

> "The Director-General initiates the process of formulating WHO's budget and establishes guidelines ... Later he compiles the proposals of the headquarters staff and the regional offices. At both stages he has opportunities to make important judgments about allocations among functions and regions. The formal position of the Director-General makes him an initiator, controller and vetoer as far as programmatic decisions are concerned."

The minutely detailed budgets proposed by the Director-General were seldom altered either by the Board or by the Health Assembly; moreover, after they had been approved, he had considerable discretionary authority to transfer funds from one programme to another and from country to country as need and opportunity dictated.

Changes in WHO policies were less likely to be impeded by long-established career staff than in many other large administrations. Relatively few had career service appointments in comparison with some other international organizations. From the time of WHO's foundation, a continuing turnover of personnel had been considered helpful in sustaining a high level of professional expertise. Thus, in 1969, only 20% of professional staff at Headquarters and the regional offices and about 5% of those working in field projects had career service appointments (Jacobson, 1973). In the same year, only 29% of the staff had served in WHO for more than 5 years.

For these reasons, WHO's limited financial support for smallpox eradication prior to 1967 (see Chapter 9) reflected the concerns and priorities of the Director-General at least as much as those of the Health Assembly. His attitude in turn reflected, in large measure, his scepticism as to the possibility of achieving global smallpox eradication until basic health services in all countries had been greatly strengthened, a scepticism shared by many scientists and health officials at that time. His doubts had been reinforced by the recommendation of the WHO Expert Committee on Smallpox (1964), discussed in the preceding chapter, which implied that everyone would have to be vaccinated to ensure eradication. Since, for example, there were tribes in the Amazon basin with which national authorities had little or no contact, it was apparent that universal vaccination was not then possible. For the Organization to be committed to an unattainable objective when, at the same time, its only other global eradication programme—that for malaria—was in serious difficulty, could jeopardize WHO's technical credibility. Moreover, the Director-General foresaw the possibility of another single-purpose eradication programme diverting national and international resources and attention from the important, but difficult and less glamorous, task of developing basic health services. He frequently pointed out that, if additional funds were to be allocated to smallpox control, they should be provided in the form of voluntary contributions by the industrialized countries, which would benefit by having fewer imported cases of the disease to deal with.

The decision, in 1966, by the Nineteenth World Health Assembly to establish a special allocation for smallpox eradication in the Organization's regular budget required WHO to undertake a more vigorous programme, but the additional funds did not allay the Director-General's concerns about the Intensified Programme's prospects of success.

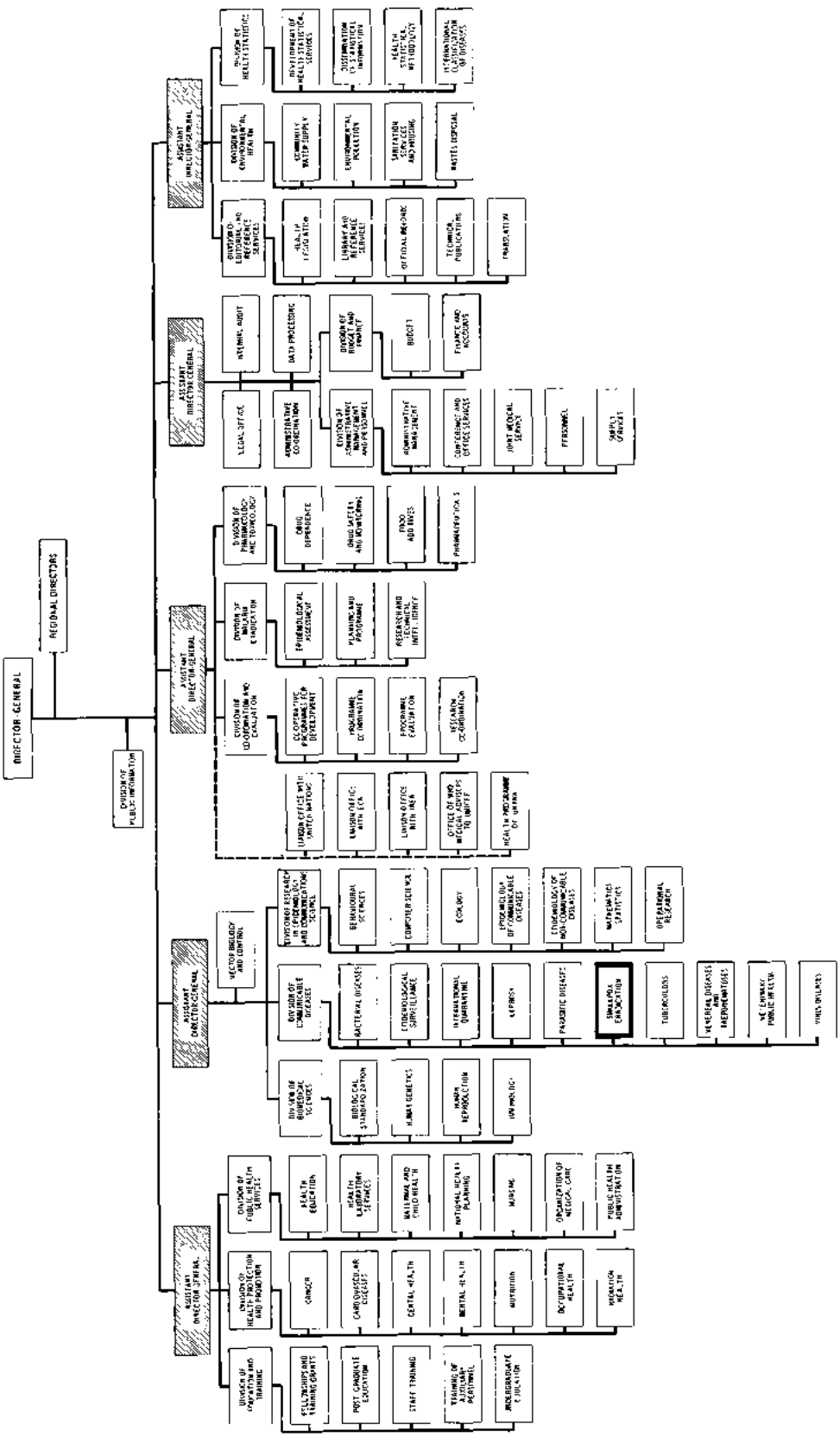


Fig. 10.2 Organizational structure of WHO Headquarters, December 1967.

Plate 10.1. Halfdan T. Mahler (b. 1923) took office as Director-General of WHO in July 1973. His long career in international public health had included almost 10 years as a senior WHO officer with the Indian national tuberculosis programme. This involved the application of methods of operations research that proved valuable when, as Chief of the WHO Tuberculosis unit, 1962–1969, he worked with the Smallpox Eradication unit to overcome the problems of the simultaneous administration of BCG and smallpox vaccines. He had been an Assistant Director-General of WHO from 1970.

WHO Programme Management in Geneva

The management and supervision of technical programmes at WHO Headquarters differed from what an organizational chart (Fig. 10.2) might suggest, as is indeed the case with many organizations. During Dr Candau's term of office as Director-General, technical programmes at WHO Headquarters were usually monitored by the Director-General and the Deputy Director-General, Dr Pierre Dorolle, through direct contact with the chiefs of the respective technical units. The senior intermediate positions in this inter-governmental organization—assistant directors-general and directors of divisions—had many representational duties and were often relatively little concerned with the day-to-day activities of the technical units. Over the 20-year period during which Dr Candau was Director-General, the Organization grew in size and the number of activities and technical units multiplied, making direct supervision of each of them increasingly difficult. Smallpox eradication programme staff seldom met the Director-General until Dr Halfdan Mahler assumed the post in 1973. Contacts with the responsible assistant director-general were likewise uncommon before Ladnyi's appointment to this position in 1976. Among those who served as directors of the Division of Communicable Diseases, Dr Karel Raška, who held this post until early 1970, took a particular interest in smallpox eradication and actively supported the programme.

The Smallpox Eradication unit had, of necessity, a closer, continuing relationship with those responsible for WHO's administration and finance. Until 1971, the Assistant Director-General responsible for this area, Mr Milton P. Siegel, an active proponent of smallpox eradication, directed these activities and those reporting to him took a similar interest in the programme. Both during and after his period of tenure, most of them went out of their way to provide help and guidance.

Throughout much of the smallpox eradication programme, the unit, as far as the management of its technical activities was concerned, functioned relatively autonomously. This meant that it could alter smallpox programme policies and make other decisions quickly, but it made it more

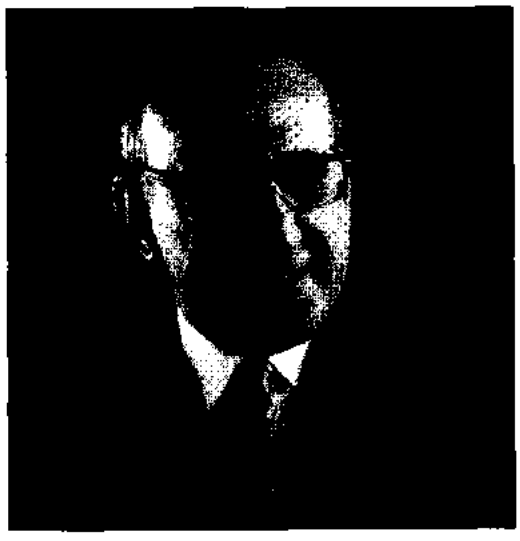


Plate 10.2. Milton P. Siegel (b. 1911). Assistant Director-General of WHO responsible for administrative and financial matters, 1947–1971.

Plate 10.3. Administrative staff at WHO Headquarters who played an especially important part in supporting the smallpox eradication programme. **A:** Adriano M. Imbruglia (b. 1925), Chief, Budget, 1971–1984. **B:** Irwin T. Brooks (b. 1916), Chief, Supply Services, 1968–1977. **C:** Alistair J. S. Taylor (b. 1923), Chief, Administration and Finance, WHO Regional Office for South-East Asia, 1972–1975; then Chief, Personnel, 1975–1983. **D:** John F. Carney (b. 1920), Chief, Finance and Accounts, 1972–1980.

difficult to implement the necessary changes and to persuade regional directors, government officials and donor agencies of the programme's need for support.

The Smallpox Eradication Unit in Geneva

The Smallpox Eradication unit in Geneva consisted throughout most of the programme of only 10 persons—4 medical officers, 1 administrative officer, 1 technical officer and 4 secretaries. Even this number had originally been considered excessive by senior WHO staff, who then envisaged the unit's activities as consisting of little more than ensuring that each country received adequate resources for conducting mass vaccination campaigns (see Chapter 9). During the first year of the Intensified Programme, however, it became apparent that far more than this was required and, indeed, that additional personnel would be useful. However, requests for additional staff were rejected, in part because of pressures by WHO Member States to limit the size of Headquarters staff. But short-term consultants could be recruited, and in 1968–1969, Dr Gordon Meiklejohn served on the staff during a sabbatical year's leave from the University of Colorado; in 1969–1970, Dr Paul Wehrle, on similar leave from the University of Southern California, also worked in the unit. Every year subsequently, each undertook special tasks on behalf of WHO for 4–6 weeks during his university vacation.

Some compensation for the dearth of staff was provided by the fact that many of those in the Headquarters Smallpox Eradication unit served for long periods; this ensured continuity and consequently a greater ability to anticipate the problems of the Organization and of governments in the endemic countries (see Table 10.1).

Late in 1970, an interregional team of 3 additional medical officers was authorized to provide short-term emergency assistance wherever required and to help in establishing surveillance programmes where these were lacking. One was recruited and assigned to Ethiopia, in which that greatly understaffed programme was just beginning, and 2 to West Pakistan when that region was divided into 4 provinces with 4 essentially autonomous smallpox programmes (see Chapter 14). As their presence in these assignments continued to be necessary, they were effectively lost to the Headquarters complement, though remaining chargeable to the Headquarters budget since the Regional Office for the

Table 10.1. Length of service and relevant previous experience of the professional staff of the Smallpox Eradication unit at WHO Headquarters, 1966–1987

Name	Position	Period	Previous experience
Dr D. A. Henderson	Chief Medical Officer	1966–1977	
Dr Isao Arita	Medical Officer	1965–1977	WHO adviser in Liberia, 1963–1965
	Chief Medical Officer	1977–1985	
Dr Zdeněk Ježek	Medical Officer	1980–1985	WHO Smallpox Eradication and Epidemiological Advisory
	Chief Medical Officer	1985–1987	Team, South-East Asia Region, 1972–1977; WHO adviser in Somalia, 1977–1979
Dr Ehsan Shafa	Medical Officer	1971–1977	WHO Regional Adviser on Smallpox Eradication, Eastern Mediterranean Region, 1967–1971
Dr Stephen Falkland	Medical Officer	1966–1969	
Dr Georgij Nikolaevskij	Medical Officer	1967–1971	
Dr Anatolij Slepushkin	Medical Officer	1971–1976	
Dr Joel Breman	Medical Officer	1977–1980	AID adviser in Guinea, 1968–1970
Dr Alexander Gromyko	Medical Officer	1977–1983	WHO short-term consultant in India, 1974
Dr Lev Khodakevich	Medical Officer	1983–1986	WHO adviser in India, 1973–1977, and in Ethiopia, 1978–1979
Mr John Copland	Administrative Officer	1966–1977	
Miss Ija Jurjevskis	Technical Officer	1967–1969	
Mrs Linda Licker	Technical Officer	1969–1970	
Mr John Wickett	Technical Officer	1970–1977	
	Administrative Officer	1977–1979	
	Consultant	1983–1987	
Mr Robert Evans	Technical Officer	1978–1979	AID adviser in Nigeria, 1968–1970
	Administrative Officer	1980	
Mr James Magee	Public Information Officer	1978–1980	

Eastern Mediterranean stated that it had no funds with which to take them over. Other efforts to increase the size of the Headquarters Smallpox Eradication unit were unsuccessful. In consequence, the few professional staff based in Geneva of necessity undertook a wide range of activities both at Headquarters and in the field. As the programme progressed, they had to travel more and more, to the point that most were in travel status for 50–70% of the time.

A partial listing of the activities undertaken by the unit gives some insight into the nature of day-to-day operations. In the interests of the morale of field staff and the acceleration of operations, priority was given to all communications from the field, the aim being to respond to queries or requests within 48 hours of receipt. A surveillance report was prepared for publication every 2–3 weeks in the *Weekly epidemiological record* and more extensive summary reports on the programme twice a year. Voluntary contributions were repeatedly sought through special mailings and visits to governments and other potential donors. Arrangements were made for the testing of vaccine and for its shipment to a central depot in Geneva. Stocks of vaccine, bifurcated needles, jet injectors, kits for the collection and dispatch of specimens and training aids were kept in Geneva and sent on request, to countries. Specimens from patients were received weekly from different countries, repacked and sent to reference laboratories for testing; the results were sent by telex to those submitting the specimens (see box). Each year 1–2 international meetings were arranged for senior smallpox eradication programme staff from regional groups of endemic countries, as well as annual conferences of WHO's regional smallpox advisers, biennial meetings of the research group concerned with monkeypox and related problems, meetings of the WHO Expert Committee and the WHO Scientific Group on Smallpox Eradication, and a special meeting dealing with vaccine production. Various training and educational instruments were prepared—manuals, posters, slide series, teaching exercises and films. An extensive correspondence was conducted on the recruitment of personnel, regional and national budgets and programmes, and the procurement of supplies and equipment. Press releases were prepared and media queries answered. Reports from field staff dealing with their work and observations were edited and published twice a month.

Plate 10.4. Participants in the meeting of the WHO Expert Committee on Smallpox Eradication in November 1971. The chairman (*right*) was Francis C. Grant (b. 1924) of the Ministry of Health of Ghana, who had been a smallpox eradication consultant for WHO in Burma in 1970. The rapporteur was Paul F. Wehrle (b. 1921), a United States professor of paediatrics who had helped to establish the global eradication programme while serving as a WHO consultant in Geneva, 1969–1970.

Because of the heavy travel commitments of the unit's staff, there was insufficient time to perform all these functions well. Had there been adequate manpower, the following 3 activities, in particular, could usefully have received more attention and this, almost certainly, would have reduced the time required to achieve eradication: (1) field studies to define more precisely the status and epidemiology of smallpox in different areas and to evaluate alternative methods of smallpox control; (2) field demonstrations, extending over 2–3 months, of surveillance–containment methods; and (3) personal contacts with potential donors to explain the programme and to seek support.

The Smallpox Eradication unit had comparatively few collaborative relationships with other technical units at WHO. One other unit with which it worked closely was that responsible for implementing the provisions of the International Health Regulations. This unit received weekly telegraphic reports of cases of the quarantinable diseases, including smallpox, and published them in the *Weekly epidemiological record*. These activities are described below, in the section

Plate 10.5. Staff of the Smallpox Eradication unit at WHO Headquarters. **A:** Donald Ainslie Henderson (b. 1928), Chief, 1966–1977. **B:** Isao Arita (b. 1926), Medical Officer, 1965–1976; then Chief, 1977–1985. **C:** John S. Copland (b. 1930), Administrative Officer, 1967–1977. **D:** John F. Wickett (b. 1944), Technical Officer, then Administrative Officer, 1970–1980, and consultant, 1983–1987. **E:** Susan E. Woolnough (b. 1948), secretary to Henderson and Arita, 1970–1985. **F:** Celia I. Sands (b. 1945), secretary, 1969–1981.

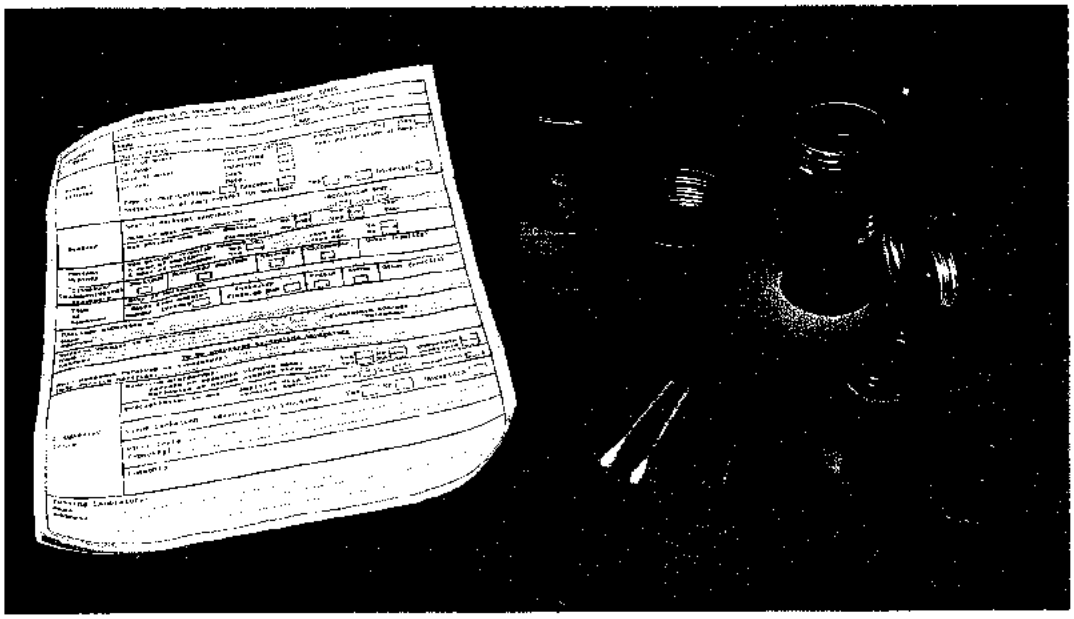


Plate 10.6. Kit provided by WHO for the collection and dispatch of virological specimens.

entitled "Surveillance and notification of smallpox cases". Collaboration with such units as those dealing with health education and maternal and child health would have been logical and potentially productive but most of them were small, with only 2 or 3 professional staff, few of whom were directly concerned with field operations. The only programme of substantial size and with extensive field activities was that for malaria eradication, but by the mid-1960s it had begun to encounter major problems which fully occupied its staff. The only other immunization programme, until 1975, was that for tuberculosis, which was the responsibility of the Tuberculosis unit. However, the staff of that unit were also few in number and much of their time was devoted to field trials aimed at assessing the efficacy of BCG vaccination.

WHO Regional Offices

The WHO regional offices were positioned administratively between WHO Headquarters and countries and were expected to play a major role in the development and coordination of all types of country programmes in their respective regions. For them, the Intensified Smallpox Eradication Programme differed from others for which they were responsible in that it required more or less simultaneous activities in all countries, both to monitor the occurrence of smallpox and to undertake programmes to eradicate the disease or to detect and contain importations. Its needs were different, therefore, from those of tuberculosis control or maternal and child health, for example. Programmes such as these were often country-specific, and it was usually of little moment to the region as a whole or to other countries whether one or more countries did or did not undertake special activities or whether a given disease was widely prevalent elsewhere or not. It might seem that experience acquired in malaria eradication would provide a model, but it did not. National malaria eradication programmes had been implemented with WHO assistance in South America and Asia but in only one country of sub-Saharan Africa (Ethiopia). Most of the smallpox-affected countries that also had endemic malaria had not progressed beyond the "attack phase", in which systematic spraying was the primary activity. Even where there was surveillance it tended to be purely national in character, since knowledge of the malaria status of neighbouring countries was of little interest except in certain border areas.

Most WHO regional offices did not, at that time, initiate health programmes. Rather, they responded to requests for assistance from governments. Owing to budgetary constraints, the travel of regional office staff

Processing of Specimens from Suspected Smallpox Patients

Specimens from suspected smallpox patients from all parts of the world were sent to Geneva and, once a week, sent by air, alternately to the WHO collaborating centres in Atlanta (Center for Disease Control) and Moscow (Moscow Research Institute for Viral Preparations). This practice was followed so as not to overburden either laboratory. Most specimens were received in Geneva in collection kits designed and provided by WHO (see Plate 10.6). The kit included a stylette and swabs for taking specimens, and a screw-capped glass vial into which the specimen was to be placed and which, in turn, fitted into a screw-capped metal container. Two copies of a form providing identifying information about the patient were wrapped around this second container and the contents placed in yet a third screw-capped cardboard shipping container. When received in Geneva, only the outer container was opened, one copy of the form removed and the specimen logged in. Laboratory results were sent to Geneva from the laboratory by telex or telephone and relayed, in turn, to the responsible health administration.

Although no problems arose with this method of handling specimens in Geneva, it is seen, in retrospect, to have been less than satisfactory, since it assumed that neither the form nor the second container was contaminated with variola virus and thus capable of causing infection. However, health officials in some countries sent specimens in other types of containers, including envelopes and small boxes, which were sometimes only partially sealed. Miss Sands, who dealt with the specimens, was revaccinated every year, as were all the staff, but she opened and processed the specimens at an ordinary secretary's desk in an open room.

While unthinkable now, the system, at the time, appeared to provide reasonable safeguards against the chance infection of others in Geneva. The infection of personnel handling specimens, even in laboratories, was uncommon and, until the mid-1970s, laboratory precautions consisted in little more than the vaccination of personnel. The occurrence of smallpox in 1978 in Birmingham, England, in a person exposed to virus carried by an air duct from one room in a laboratory to another demonstrated the need for more stringent precautions.

Another concern present throughout the course of the programme was that of the possible loss of specimens in shipment. Thanks to a rigorous, continuing check of bills of lading against receipt of shipments, this did not occur, but, as a precaution, specimens sent from Geneva to Moscow and Atlanta were packed in large containers which would be less likely to be mislaid.

tended to be restricted. Efforts to persuade WHO regional directors that the needs of global smallpox eradication called for a somewhat different approach met with only limited success, varying from region to region. The Region of the Americas and the Eastern Mediterranean Region immediately appointed full-time advisers on smallpox eradication, and a year afterwards two medical officers in the South-East Asia Region were given full-time responsibility for smallpox eradication. In these regions, programme planning, the recruitment of staff and the procurement of supplies and equipment were most efficiently conducted. In the African Region, however, until certification activities began, responsibilities for the smallpox eradication programme were assigned as a part-time responsibility to the adviser on tuberculosis or on all communicable diseases. Not only did this region include more countries than any other, with some of the world's least developed health systems but, in addition, communications between the regional office and countries were poor and travel was difficult. As is described in the chapters dealing with field operations, there were continuing problems of every type in endeavouring to develop and support national programmes. In all regions, however, a lack of personnel in the regional offices and the customary constraints on their travel handicapped programme development. Where only a single adviser was involved, his absence on leave or duty travel meant that communications often went unheeded and

other activities, such as recruitment and the procurement of supplies and equipment, slowed down or ceased altogether. As a result, Headquarters staff travelled far more frequently and extensively than might otherwise have been necessary for a programme having a regional structure.

The regional offices were at that time likewise largely unaccustomed to the coordination of plans, needs and resources within a global context. To try to achieve better coordination, the Headquarters Smallpox Eradication unit held annual meetings for those responsible for smallpox eradication in each region to discuss goals, plans and progress. At the meetings, priorities were decided and needs identified, including funds, vaccine, vaccination instruments, personnel, and training aids. Such meetings were usually held in conjunction with a WHO-organized multinational meeting of programme staff, at which strategy and recent field observations were also discussed. Whatever the venue, it was always necessary to make a special appeal to one or several of the regional directors to obtain permission for advisers to attend, a permission which was usually but not always granted and then only on the condition that Headquarters funds would be used for travel. Although the meetings proved invaluable, it was never possible to achieve a rational allocation of funds, as will be discussed later.

WHO Representatives in Countries

The WHO representatives in countries provided the point of contact between WHO and the countries; they were assigned to most developing countries to assist in formulating policy and developing projects, and to provide administrative and technical guidance to WHO-supported programmes. Some of them had had many years of experience in international health work, but most were recent recruits who had held senior positions in their own national health services. They took up their positions after a short briefing, largely of an administrative character, and usually met their regional directors and other WHO representatives once or twice a year. Few were experienced or knowledgeable in smallpox eradication and, because of their

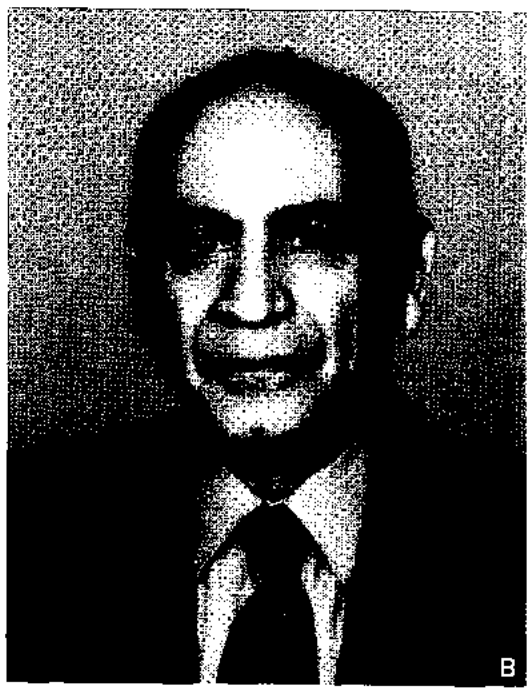


Plate 10.7. **A:** Nicole Christiane Grasset (b. 1927) served as adviser for smallpox eradication in the South-East Asia Region of WHO, 1970–1976, succeeding Jacobus Keja who had been an adviser there from 1967. **B:** Ahmad J. Hajian (b. 1920) was the smallpox eradication adviser in the Eastern Mediterranean Region of WHO, 1971–1977, replacing Ehsan Shafa (Plate 10.12).

numerous other responsibilities, few could make any substantial contribution specifically to the Intensified Programme.

Smallpox Eradication Programme Staff

The quality and commitment of international staff proved to be one of the most important factors in the successful eradication of smallpox, and considerable time and effort were expended by the Smallpox Eradication unit on recruiting them. The task was not an easy one, however. Epidemiologists with experience in infectious disease control were particularly desirable because of the need to initiate and foster epidemiological surveillance. In 1967, however, few were available, and of those who were, almost none had ever seen cases of smallpox. Most were recruited on the strength of their experience in the management of health programmes, special consideration being given to basic competence and motivation. Specialized training in smallpox eradication methods would have equipped them better for their assignments but many difficulties were encountered in providing it. Thus, adequate numbers of fully qualified staff did not become available until the Intensified Programme was well advanced.

The provision of special training programmes in smallpox eradication proved impracticable, except for international and senior national staff working in the programme conducted with United States assistance in western and central Africa. For these, from 1966 onwards, the Communicable Disease Center (which has been renamed on several occasions and is now the Centers for Disease Control and widely known simply as CDC) provided a 4-week training course every year. Only a few WHO staff attended because WHO regional offices were unaccustomed to providing specialized training for newly recruited staff, as most were already experienced in the work that they were expected to do. In any event, by 1970, because of the early interruption of smallpox transmission in western and central Africa (see Chapter 17), the CDC course had so changed in character as to be of limited value for those engaged in the early phases of an eradication programme. WHO had provided specialized training at malaria eradication centres, but smallpox eradication was widely perceived as consisting in little more than mass vaccination, for which little specialized knowledge was thought to be needed. A WHO-conducted interregional training course was not available as an option because most regional offices did not wish to incur the expense of sending new advisers to Geneva for briefing, Most new staff therefore took up their positions with a briefing of a week or less in their respective regional offices, provided that there was a smallpox adviser in the region to brief them and that he was not then on duty travel. Not until 1974, when the number of international staff increased substantially, did WHO begin to provide organized training programmes for its staff. These were conducted at national level, first in India and then in Bangladesh and Somalia, concurrently with their large-scale intensified programmes.

Other methods were used to educate and orientate newly recruited staff. It was believed and subsequently confirmed that the clinical characteristics of smallpox could soon be learned after arrival in the country. For this purpose, the following were available: the WHO Handbook; a 4-colour, 8-page printed folder showing pictures of smallpox in African patients and describing the course of the disease (1969); sets of teaching slides showing smallpox in African patients (1969) and Asian patients (1971); and a large wall chart showing the appearance of smallpox and chickenpox rashes at various days after the onset of the disease (1970).

The epidemiological principles underlying proper surveillance and containment proved more difficult to convey. Many different approaches were used, beginning with the instructions provided in the WHO Handbook. Later, two case histories with syllabuses were developed, one dealing with techniques for the investigation and control of an outbreak (SE/71.1) and the other with surveillance–containment measures to be taken in an area with a population of about 2–3 million (SE/72.7). (The latter was adapted for use as a case history by the Harvard School of Business Administration.) On-site tutorial training was provided by WHO Headquarters and some regional smallpox eradication programme staff, and periodic intercountry meetings were structured to emphasize surveillance–containment methods and to illustrate approaches. Reports and materials distributed every 2–3 weeks in the so-called "biweekly mailing" (see below) also proved useful. All these efforts, however, fell short of what was required, as was shown by

the length of time required to implement surveillance–containment programmes in most areas and the fact that some African countries were never fully successful in doing so.

Difficulties in communicating with staff working in the field also hampered efforts to develop expertise and solve problems. All communications from Headquarters had to be routed through the appropriate regional office, logically the principal point of contact for the countries in that region. Where there was a full-time smallpox adviser and the region comprised few countries—South-East Asia, for example—reasonably close contact with field staff and programmes in the countries was possible. Where there was no full-time adviser and the countries in the region were numerous, as in Africa, communications were difficult and special measures were necessary. The nature of the problems may be illustrated by the fact that, if a letter was sent from Geneva to the regional office inquiring about the status and needs of a national programme, it was usually necessary for a regional adviser to prepare a special letter for the signature of one of his superiors or the regional director. After drafting and revision, the letter would then be sent to the WHO representative, who would contact either the WHO smallpox adviser or the national health authority. When the information had been obtained, a letter of reply would be prepared and the procedure repeated in reverse. Since the mail was slow and unreliable almost everywhere, it was exceptional to receive a reply to a query from Geneva in less than several months, if it was received at all.

This problem was overcome to some extent by arranging for copies of important correspondence and telex messages to be sent direct from a country to Geneva, and for Headquarters staff, likewise, to send a copy of the reply to the country, the original being sent to the regional office as prescribed. This was of crucial importance in many instances, for example, in dealing within days with an acute shortage of vaccine in Uganda at a time when a telex message "through the proper channels" took 8–9 weeks. Although this approach violated the prescribed procedures, field staff frequently noted that the immediate responsiveness of Headquarters staff to their requests and queries played an important role in sustaining morale and giving impetus to the programme.

Up to the end of 1967, WHO smallpox eradication programme staff throughout the world numbered less than 30. Additional WHO staff were required as national programmes began but recruitment proceeded slowly, the ability and dedication of recruits varying greatly. Except for those who were assigned to Geneva or were members of an interregional team, recruitment and selection were the responsibility of the regional offices, whose personnel services operated independently of Headquarters. Headquarters smallpox eradication staff endeavoured to assist the regional offices in identifying suitable candidates through personal contacts and the screening of applications received in Geneva, but proposals at first were as often ignored as accepted. An especially discouraging episode was the assignment by one regional office of a particularly well qualified candidate to an entirely different programme after months of work by Headquarters smallpox eradication staff to recruit him to WHO for work on smallpox eradication.

Because of the problems, such impetus as the programme possessed during its first few years was provided by a very small number of qualified WHO staff, the staff of the programme conducted with United States assistance in western and central Africa, and national staff. Among the WHO staff were Dr Pierre Ziegler, who worked in Zaire; Dr Celal Algan in Rwanda; Dr Karel Markvart in East Pakistan; Mr Henry Smith in Kenya; Mr Leo Morris in Brazil; Dr Jacobus Keja in the Regional Office for South-East Asia; and Dr Ehsan Shafa in the Regional Office for the Eastern Mediterranean. Eventually, however, a reasonably satisfactory collaborative relationship with respect to recruitment evolved between Headquarters and two of the four Regions concerned.

At first, many international staff were transferred from other projects which were not progressing well or in which the staff had proved unsuitable. Over a number of years, some of the less effective and less industrious staff were transferred by WHO to yet other programmes or did not have their contracts extended. A stated policy of the programme that all smallpox eradication staff should spend at least one-third of their time in the field facilitated this weeding-out process, the policy being monitored, where necessary, by review of daily tour diaries.

Especially helpful in the recruitment of more capable staff were senior epidemiolo-

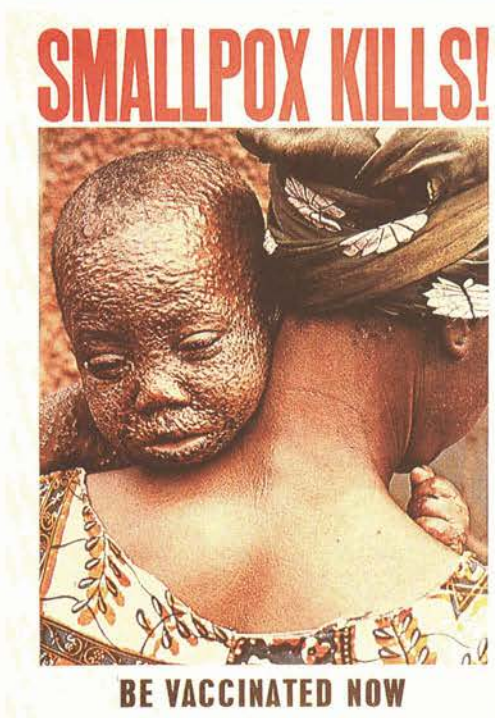


Plate 10.8. **A:** A pictorial guide to the diagnosis of smallpox in African patients, published by WHO in 1969, which included pictures of patients with chickenpox for comparison. **B** and **C:** WHO issued posters with ample white space in which messages could be overprinted in local languages. The patient in **B** was photographed in Zaire, in **C** in Pakistan. The reward poster, **C,** overprinted in Indonesia, says: "5000 rupiahs to the first person who discovers a real case of smallpox. Please report to the head of the community or the local health inspector and ask about the terms."

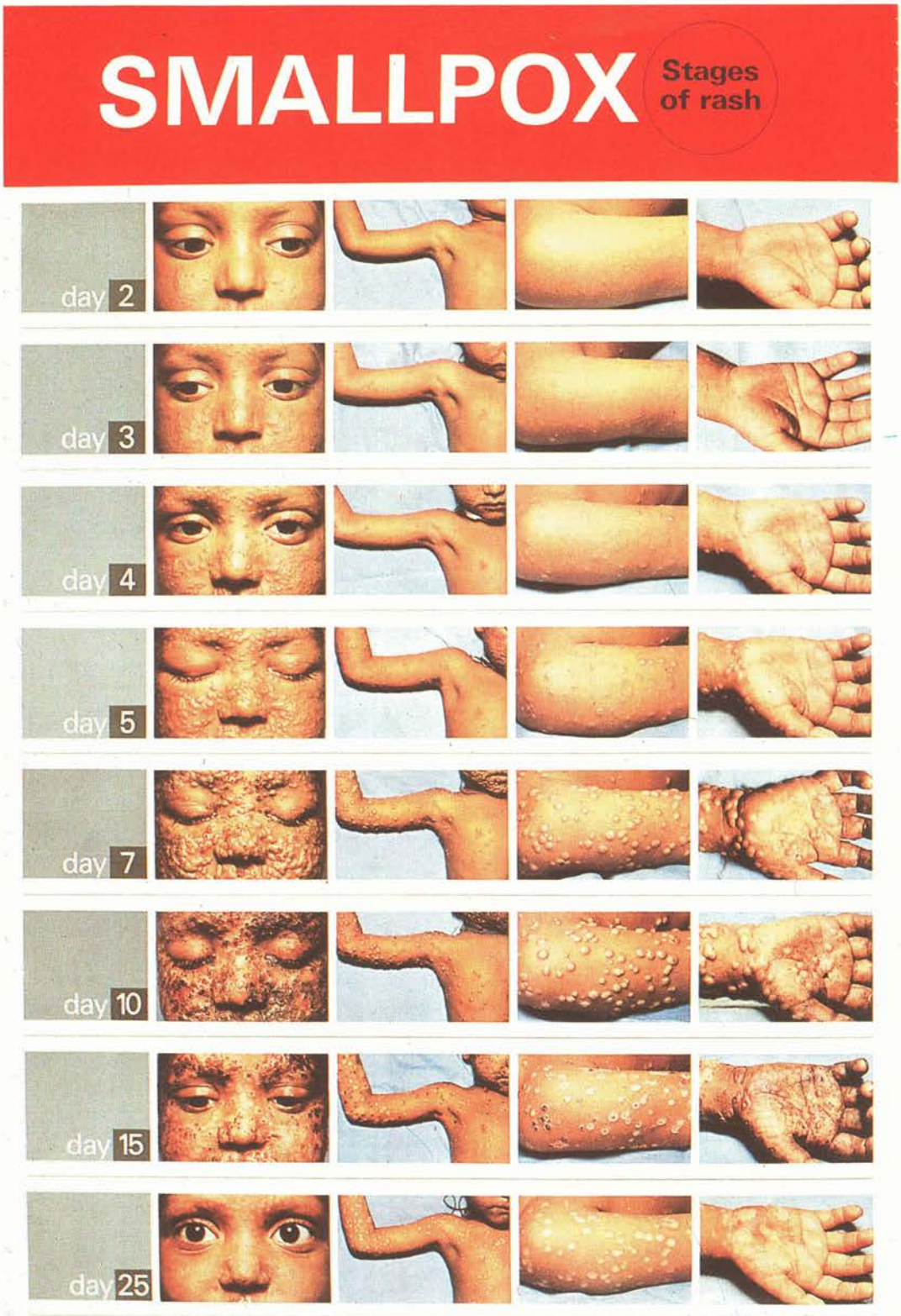


Plate 10.9. The left-hand portion of a large wall poster that contrasted the rashes of smallpox and of chickenpox on 4 areas of the body. English, French and Portuguese versions of this poster were prepared in 1970.

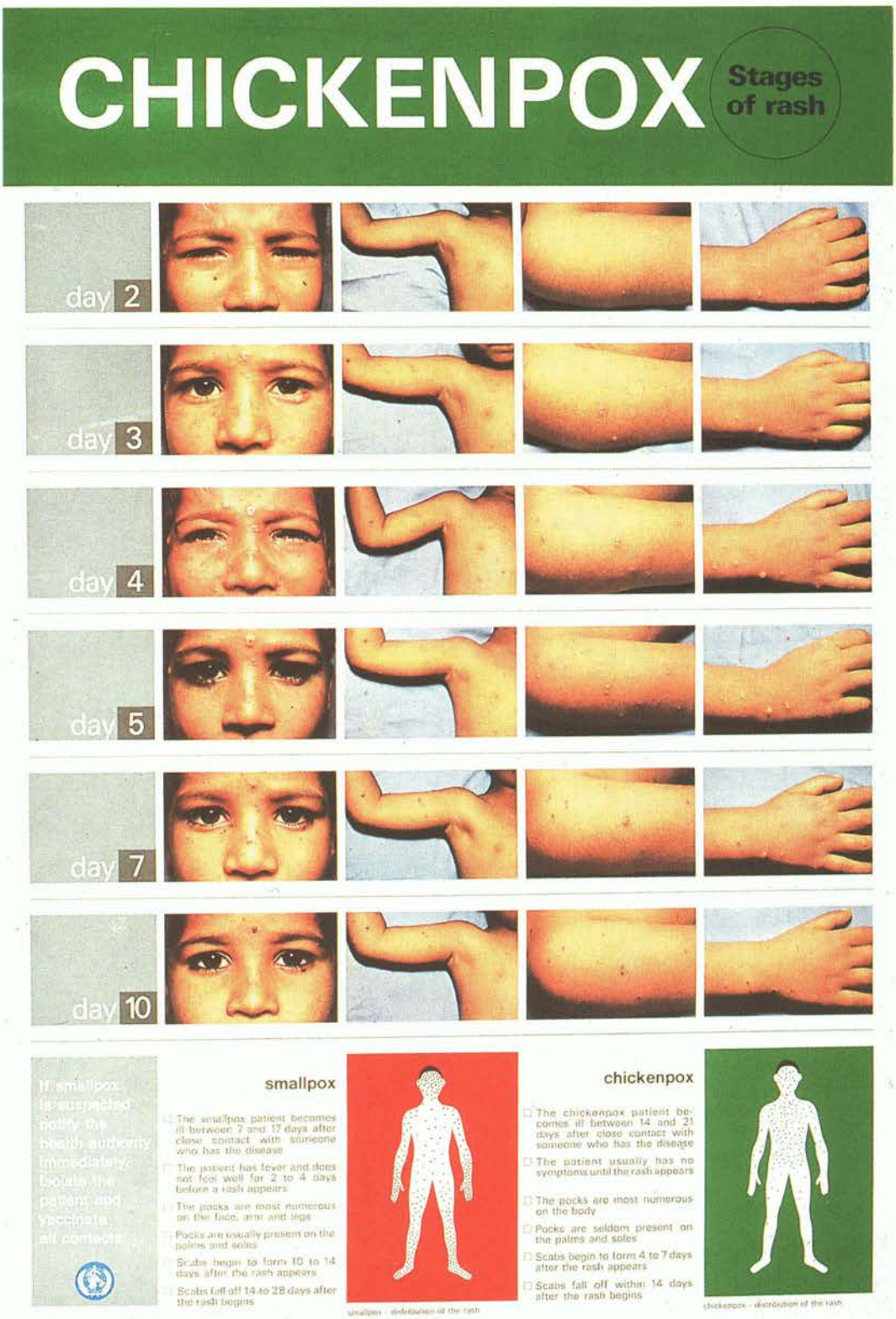

CHICKENPOX
Stages of rash
day 2
day 3
day 4
day 5
day 7
day 10
If smallpox is suspected notify the health authority immediately. Isolate the patient and vaccinate all contacts
smallpox
The smallpox patient becomes ill between 7 and 17 days after close contact with someone who has the disease
The patient has fever and does not feel well for 2 to 4 days before a rash appears
The pocks are most numerous on the face, arms and legs
Pocks are usually present on the palms and soles
Scabs begin to form 10 to 14 days after the rash appears
Scabs fall off 14 to 28 days after the rash begins
smallpox - distribution of the rash
chickenpox
The chickenpox patient becomes ill between 14 and 21 days after close contact with someone who has the disease
The patient usually has no symptoms until the rash appears
The pocks are most numerous on the body
Pocks are seldom present on the palms and soles
Scabs begin to form 4 to 7 days after the rash appears
Scabs fall off within 14 days after the rash begins
chickenpox - distribution of the rash

Plate 10.10. The right-hand portion of the poster in Plate 10.9. The text and drawings at the bottom gave simple indications by which to distinguish the signs and symptoms of smallpox from those of chickenpox.

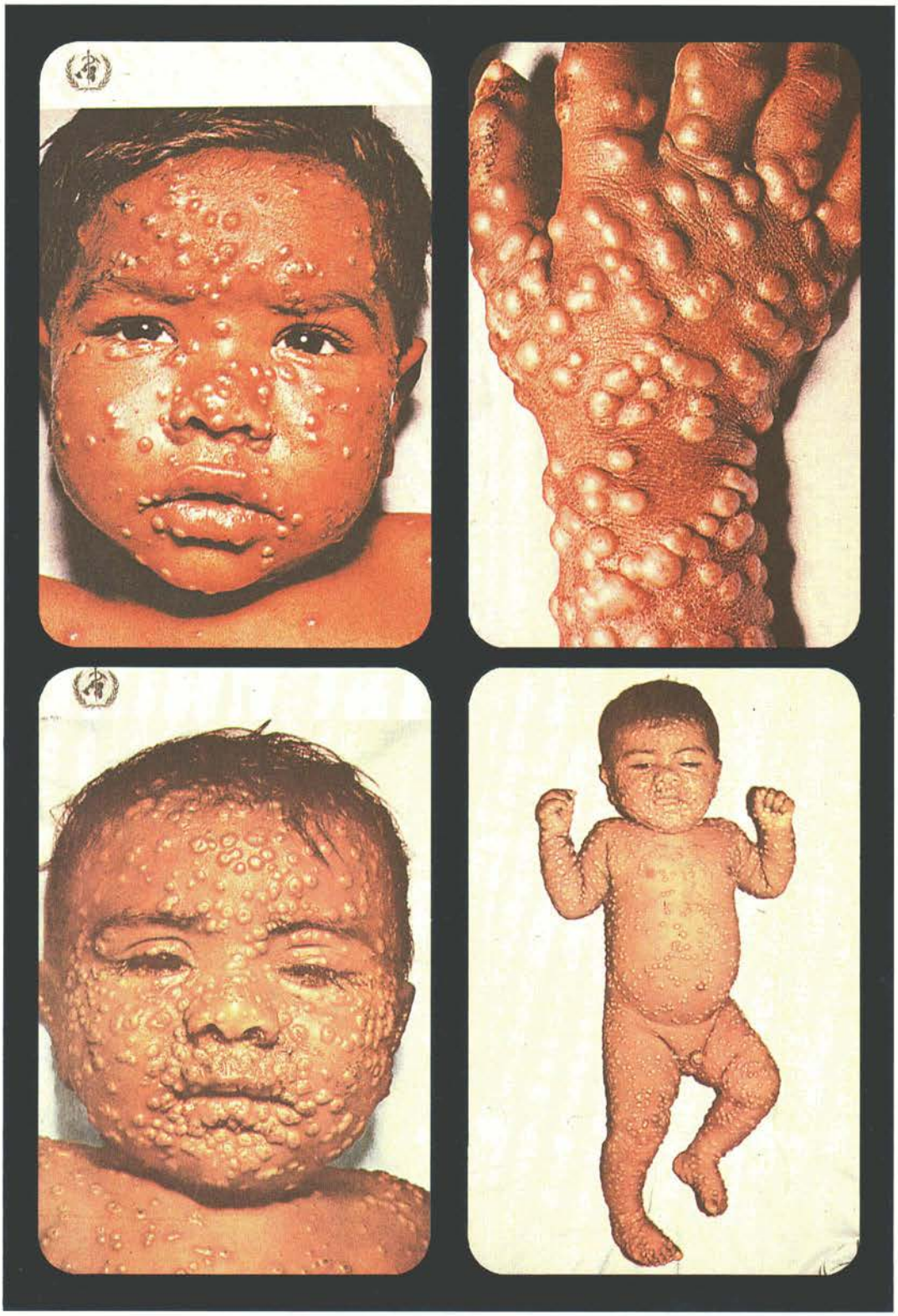


Plate 10.11. The front and back of two versions of the shirt-pocket-size WHO smallpox recognition card produced in 1972. They were first used in India, and tens of thousands were eventually distributed to search workers throughout the subcontinent. The first version (upper pictures) was selected to portray a patient with relatively mild smallpox; it is a reduced version of the larger card shown in Plates 10.29 and 10.30.

Plate 10.12. **A:** Zdeněk Ježek (b. 1932) was attached to the WHO Regional Office for South-East Asia in 1972, working for smallpox eradication in India. He later served in Somalia, before joining the Smallpox Eradication unit at WHO Headquarters in 1980 and succeeding Arita as Chief of the unit in 1985. **B:** Ehsan Shafa (b. 1927) was the smallpox eradication adviser in the Eastern Mediterranean Region of WHO, 1967–1971, and then served with the Smallpox Eradication unit at WHO Headquarters until 1977.

gists from a number of countries who were interested in the programme and aware of its demands and who screened and referred former students and colleagues. Such epidemiologists included Dr Karel Raška, Czechoslovakia; Dr Jan Kostrzewski, Poland; Dr Holger Lundbeck, Sweden; Dr Viktor Zhdanov, USSR; and Dr Paul Wehrle, USA. From early in 1972, when smallpox epidemics unexpectedly occurred in Bangladesh, until 1977, Dr David Sencer, then Director of CDC, made available the services of 5 full-time CDC staff, and from 1974, the High Institute of Public Health in Alexandria, Egypt, provided a number of faculty members and former students.

As the programme progressed, the number of capable staff with field experience gradually increased, and those who had successfully worked in their own national programmes were recruited for service in other countries. These included staff from Afghanistan, Bangladesh, Brazil, India, Indonesia, Nepal, Pakistan, the Sudan, Togo and Yemen.

International volunteers contributed significantly, both while serving as such and subsequently when recruited as consultants or staff. Arranging such volunteer support was difficult, however, because WHO policy until the mid-1970s was that volunteer assistance had to be arranged strictly between recipient and donor governments, WHO staff not being allowed to assist in the process. Unofficial contacts and private correspondence, however, served to facilitate the assignment of United States Peace Corps volunteers in Afghanistan, Ethiopia and Zaire; volunteers from Japan and Austria, who served in Ethiopia; and British volunteers from OXFAM (a British private charitable organization), who worked in India and Bangladesh. Regrettably, an offer by Sweden, in 1970, to assign young medical officers at Swedish government expense to WHO itself had to be rejected by the Organization for policy reasons.

Until 1973, international staff assigned to a country rarely numbered more than 1–4, with the exception of large countries and those with an especially difficult terrain and a shortage of national personnel—Afghanistan, Bangladesh (from 1972), Ethiopia, Nigeria and Zaire. From 1973 onwards, increasingly large numbers of international staff worked in Bangladesh and India and later in Ethiopia and Somalia as more funds became available and efforts were intensified to achieve eradication in the shortest possible time. Throughout the course of the global programme, however, international staff of all types at any given time never numbered more than 150. In all, 687 WHO staff and consultants from 73 different countries eventually served in the programme for periods

ranging from 3 months to more than 10 years; approximately 125 others served with the programme under bilateral agreements. Most of the staff were less than 40 years of age and some less than 30, youth being an advantage where living and travelling conditions were difficult.

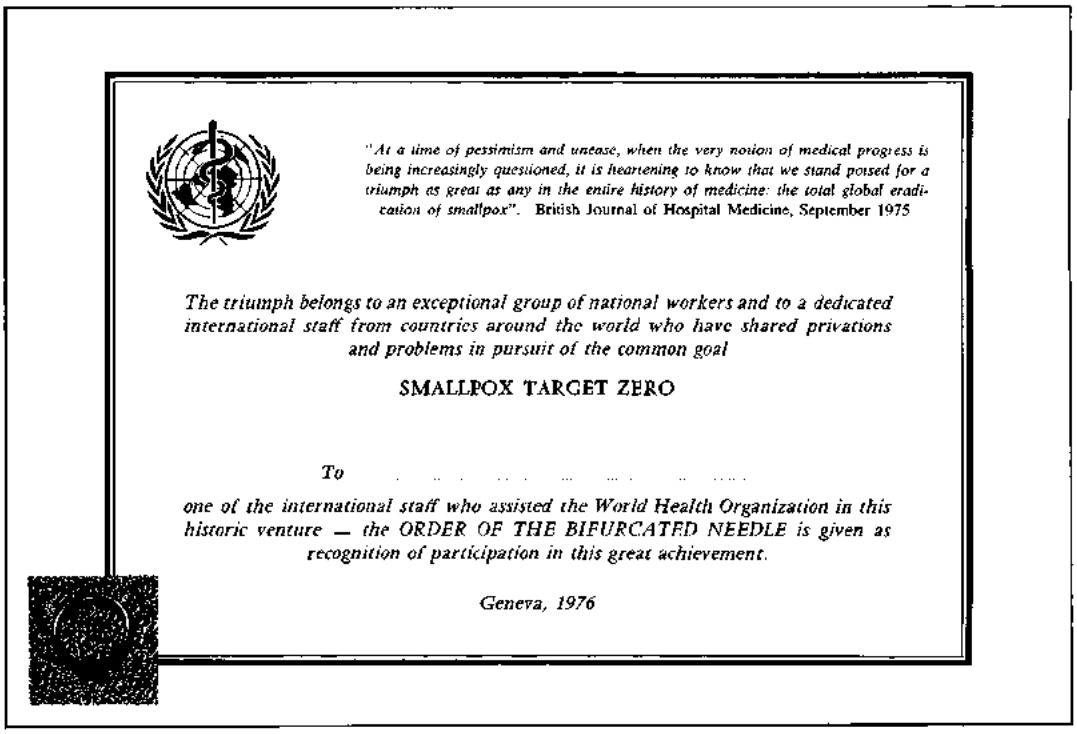
Although international staff were few, they played an important role in sustaining national government support, providing programme continuity where national leadership changed for political or other reasons, and expediting the transfer of new techniques from one programme to another. In retrospect, it may be said that few national programmes achieved much success where international staff were of poor quality, but national staff, given the necessary support and encouragement, showed themselves to possess a skill and dedication which equalled and often exceeded those of the international advisers.

OBTAINING NATIONAL AGREEMENTS TO UNDERTAKE PROGRAMMES

Although commitments assumed by governments by virtue of votes in favour of resolutions at the World Health Assembly were morally binding, WHO could not force governments to undertake programmes. Thus, although the Intensified Smallpox Eradication Programme was unanimously approved by the Health Assembly, only certain countries were, in fact, then prepared to undertake eradication programmes—much as had been the case during the period 1959–1966. Some lacked resources, while others considered that other health problems were of higher priority. Universal participation was essential if the programme was to succeed but, as described earlier, WHO's role in actively promoting and advocating a particular programme in all countries was an unaccustomed one. Malaria eradication was the only other programme in which this had been attempted but, in that programme, the necessary but substantial additional national costs had distorted health allocations, and the extent to which its secondary objective, the improvement of basic health services, had been attained had fallen far short of expectations. Mindful of this experience and doubtful of the feasibility of smallpox eradication, the Director-General cautioned his regional directors, at a meeting immediately after the 1966 World Health Assembly, against appearing to impose a smallpox eradication programme on any country. Thus, in 2 regions, Africa and South-East Asia (unfortunately also those most seriously affected by smallpox), the regional directors did not initially promote smallpox eradication programmes, assistance being provided only to countries specifically requesting it. In the Region of the Americas and the Eastern Mediterranean Region, however, eradication programmes were actively promoted from the beginning.

In the Americas, smallpox eradication was not a new objective, a regional eradication programme having been in existence since 1950 (see Chapter 9). A Regional Adviser on Smallpox Eradication, Dr Bichat Rodrigues, was appointed in 1966 to coordinate the effort, and Brazil, the only endemic country, committed itself to a national smallpox eradication programme employing what were then the new jet injectors (see Chapter 12). Vaccination campaigns in many other countries in South America began soon thereafter. In the Eastern Mediterranean Region, there were then 3 endemic countries—Ethiopia, Pakistan and Yemen—and there, also, an adviser on smallpox eradication, Dr Shafa, was immediately appointed. He successfully promoted programmes in Pakistan, Yemen and other countries of the region although, for reasons beyond his control, he was unsuccessful in Ethiopia, in which a programme did not begin until 1971 (see Chapter 21).

In the South-East Asia Region, the Regional Director shared the Director-General's belief that eradication represented an unattainable goal, given the stage of development of national health services (see Chapter 9). Responsibility for smallpox eradication was assigned to a 2-man intercountry advisory team which dealt with other communicable diseases as well and whose budget for travel was small. Little was done in the Region until Dr Herat Gunaratne was elected Regional Director in 1968; coming from Sri Lanka, a country which had eliminated endemic smallpox decades before, he saw no reason why this could not be achieved elsewhere. He therefore made the intercountry team, Dr Keja and Dr Louis Gremliza, responsible solely for smallpox eradication and, from the time of his election, played



"At a time of pessimism and unease, when the very notion of medical progress is being increasingly questioned, it is heartening to know that we stand poised for a triumph as great as any in the entire history of medicine: the total global eradication of smallpox". British Journal of Hospital Medicine, September 1975

The triumph belongs to an exceptional group of national workers and to a dedicated international staff from countries around the world who have shared privations and problems in pursuit of the common goal

SMALLPOX TARGET ZERO

To . . . . . .

one of the international staff who assisted the World Health Organization in this historic venture — the ORDER OF THE BIFURCATED NEEDLE is given as recognition of participation in this great achievement.

Geneva, 1976

Plate 10.13. The contribution of the international staff who participated in the eradication of smallpox was given sincere if informal recognition by their promotion to the mock "Order of the Bifurcated Needle", accompanied by an official-looking certificate and a hand-made lapel pin. The pins (*inset*) were fashioned from bifurcated needles in the form of an "O" to symbolize "Target Zero", the objective of the programme.

an active role in encouraging national programmes. The response was generally enthusiastic and within a year effective programmes were in progress in all endemic countries of the region except India, where the programme started later (see Chapter 15).

In the African Region, by late 1966, a number of countries had already committed themselves to national smallpox eradication programmes. These included the 20 countries of western and central Africa which were participating in the smallpox eradication and measles control programme being carried out with the assistance of the USA; Zambia, which had begun a national vaccination campaign in 1966 because of epidemic smallpox; and Zaire, whose WHO-supported activities were then coordinated by Geneva Headquarters. The other African countries did not officially express any interest in 1966 and early in 1967. This was disturbing to the staff in Geneva, but also puzzling because funds were then available to meet all the costs of the programmes except salaries for the comparatively small number of national personnel who would be required. Because WHO was prepared to provide vaccine free of charge and because many countries already employed smallpox vaccinators, it was actually cheaper for most of them to participate in the eradication programme than to continue smallpox control activities. They failed to express interest, as was later discovered, because no effort was made by the Regional Office to encourage programmes, acquaint national authorities with the programme's budgetary implications, or indicate the amount of support which could be provided by WHO; instead, the national authorities were expected to request WHO's assistance on their own initiative. The WHO representatives in the countries, as well as Ladnyi, then intercountry smallpox adviser for East Africa, were informed of this policy in September 1966. In the spring of 1967, the problem was resolved fortuitously when a member of the Headquarters Smallpox Eradication unit was given permission to visit several of the countries for the purpose of gathering information for the Director-General's report to the 1967 World Health Assembly. Although he was forbidden to

suggest to any country that a programme should be undertaken, he made the health authorities aware of the nature of the programme and the resources available and, within weeks, letters requesting WHO assistance were received from almost all of them.

By the summer of 1969, smallpox eradication programmes had begun in all the endemic countries in Africa except South Africa, Southern Rhodesia (now Zimbabwe) and Ethiopia. WHO then had no official relations with the first two of these, South Africa having ceased to participate in the Organization and Southern Rhodesia being technically still a colony of the United Kingdom, although it had unilaterally declared independence. Visits by WHO staff were not permitted and little information could be obtained about the status of smallpox or their programmes. However, neither was thought to represent a serious impediment to eventual global eradication because neither officially reported many smallpox cases and their health services were comparatively well developed. Both began special programmes in 1970 (see Chapter 20), stimulated largely by reports in the *Weekly epidemiological record*, which described excellent progress in smallpox eradication elsewhere in Africa but noted the lack of information from South Africa and Southern Rhodesia. The third country, Ethiopia, although in Africa, was served (until late in 1977) by the Regional Office for the Eastern Mediterranean and presented quite a different problem. Smallpox was widely endemic and health services were few, but malaria eradication staff and their international advisers, fearing that another programme would be a harmful distraction, persuaded government officials to refuse to discuss with WHO the implications of a smallpox eradication project. Not until late in 1969 did the government permit Henderson and Dr Shafa to visit the country. At that time, Ministry of Health officials declined to participate but the Emperor himself, who by chance had heard about the programme, intervened to commit the government and, in 1971, the last of the programmes in the endemic countries began (see Chapter 21).

Thus, although many countries needed to be encouraged and persuaded to undertake smallpox eradication programmes, these had, in fact, been initiated in all endemic countries within 5 years of the 1966 decision. It was quite another problem to ensure that the various governments were sufficiently committed for eradication of the disease to be achieved.

SUSTAINING GOVERNMENT INTEREST AND COMMITMENT

A continued high level of interest and support for the eradication programme was difficult to sustain in many countries, just as it was in WHO. Changes in governments and/or senior health personnel were often associated with differences in priorities and in levels of commitment. Smallpox was but one of many problems competing for attention and resources and, in countries in which the mild variola minor form was prevalent, it was understandably not of high priority. After the last known cases had occurred, resources were particularly difficult to obtain from recently endemic and donor countries, as well as from WHO itself, in order to continue surveillance and thus permit certification.

Role of the World Health Assembly

The World Health Assembly, convened each year for a period of several weeks, was a particularly important opportunity for promoting and sustaining interest in the smallpox eradication programme. Senior health officials from all Member States attended and, in addition to reviewing the proposed WHO budget, discussed the Organization's overall programme of work as well as specific programmes, such as that for smallpox eradication. During the debate, delegates frequently described what their own countries were doing, some asked questions of a technical nature and others took the opportunity to announce voluntary contributions. The Intensified Smallpox Eradication Programme, if included as an agenda item, might be discussed for 2–4 hours or more. Such a discussion served to focus the attention of health officials on the subject, and important principles—such as the role of surveillance and the need to use only freeze-dried vaccine—could be emphasized by the Secretariat. It also enabled government officials to hear what were often heartening or optimistic reports of progress in other countries, causing them to reexamine their own programmes. If, however, smallpox eradication was not included in the agenda as an item for

debate, it could still be discussed when the overall programme of the Organization was considered, but it was unusual for many delegates to prepare themselves to speak on the topic and the debate was usually brief.

Because the Health Assembly had identified smallpox eradication as a priority programme of the Organization and it had been on the agenda each year from 1959 to 1967, the Smallpox Eradication unit staff assumed that the topic would continue to be an annual subject for debate on which the Director-General would provide a special report to the Health Assembly. From 1968 onwards, however, it began to be omitted from the provisional agenda. The resolution on smallpox eradication adopted by the Twentieth World Health Assembly (1967), called only for the Director-General "to report further" on smallpox eradication to the Executive Board and the Health Assembly. "Further" was interpreted to mean at some time in the future and the topic was omitted from the provisional agenda of the Twenty-first World Health Assembly (1968), an action which was reversed at the request of the USSR. Resolutions adopted at the 1969, 1971, 1972, 1976 and 1977 Health Assemblies called specifically for special reports to each of the subsequent ones and for smallpox eradication to be included in their agendas. In the other years until 1977, when transmission was interrupted, smallpox eradication was the subject only of a brief general discussion in the context of the overall WHO programme. A report by the Director-General was nevertheless prepared and kept in readiness in case one was requested by delegates. To it was attached a comprehensive review of the programme's progress and status that was published twice a year in the *Weekly epidemiological record* to coincide with the January session of the Executive Board and with the Health Assembly. Although the report was not to be distributed unless requested by delegates, the interest expressed, particularly by two delegates, one from the USSR and the other from the USA (Dr Dmitrij Venediktov and Dr Paul Ehrlich, Jr, respectively), ensured that it was distributed and the programme discussed.

Surveillance Reports

Regularly published surveillance reports, both international and national, were an essential component of the surveillance process and, as experience had demonstrated in other disease control programmes, were also important in stimulating and sustaining the interest of those concerned with the programme. Such reports documented the numbers of cases reported weekly by administrative area, charted trends in incidence and in the progress of the programme, and discussed alternative strategies and tactics in

Plate 10.14. Two delegates to the World Health Assembly and members of the Executive Board of WHO who were strong advocates of smallpox eradication. **A:** S. Paul Ehrlich Jr (b. 1932), Surgeon General of the United States Public Health Service. **B:** Dimitrij D. Venediktov (b. 1929), Deputy Minister of Health of the USSR.

different areas. The first WHO surveillance reports on smallpox eradication were issued in September and December 1967, and from May 1968 onwards, they began to be published every 2–3 weeks in the *Weekly epidemiological record*, some 5000 copies being distributed to health officials and others throughout the world. The system was not established without difficulty, however, as is discussed later in this chapter in the section entitled "International surveillance reports". The WHO Regional Office for South-East Asia also issued surveillance reports from 1974 onwards, and national surveillance reports were published monthly and sometimes weekly or every 2 weeks in a number of countries.

In addition to providing information to widely scattered health staff, the reports also served to inform both public officials and the press, sometimes with unexpected consequences. When, in Brazil, Ethiopia and India, for example, better surveillance and improved reporting were accompanied by marked increases in the numbers of notified cases, national officials and the press expressed concern, and even alarm, although the increases were attributed, at least in part, to better reporting. Greater political commitment and increased resources soon followed. In other countries, interest in the programme grew significantly when national officials read of more satisfactory progress being made in other countries, some of which they believed to have health services inferior to their own.

Interregional and Intercountry Meetings of Smallpox Eradication Staff

Meetings of senior staff from different national programmes also served to sustain and stimulate the interest of governments and staff while bringing to their notice the new observations which were being made. The WHO Headquarters budget provided for at least one such meeting a year, the venue changing from year to year, as did the participants (Table 10.2). In addition, over the period 1967–1972, CDC supported a yearly conference for the countries of western and central Africa.

The first of these meetings was held in Thailand in 1967 for countries in eastern Asia. At first they were largely devoted to the presentation of reports on national programmes by the respective national directors; over time, their nature gradually changed and each country was asked to present papers illustrating specific findings, the outcome of particular strategies and interesting new approaches. The ensuing discussions made it possible to determine whether the observations made in a particular national smallpox eradication programme were of relevance to the others. Most of these reports were distributed by WHO to all concerned with smallpox eradication through the special WHO/SE, SE and SME series of mimeographed documents (see References: WHO documents); some were also published in the medical literature.

Table 10.2. WHO seminars and meetings on smallpox eradication, 1967–1978 (excluding those associated with certification of eradication)

Date	Country in which held	Participants[a]
December 1967	Thailand	13 countries of South-East Asia, Eastern Mediterranean and Western Pacific Regions
November 1968	Zaire	11 countries of southern and eastern Africa
May 1969	Nigeria	18 countries of western and central Africa (joint seminar with CDC)
November 1969	Pakistan	11 countries of Eastern Mediterranean and South-East Asia Regions
December 1970	India	11 countries of South-East Asia, Eastern Mediterranean and African Regions
September 1972	Ethiopia	4 countries of eastern Africa
November 1972	India	5 countries of South-East Asia Region
November 1972	Pakistan	4 countries of Eastern Mediterranean Region
September 1973	Ethiopia	Ethiopia and WHO Eastern Mediterranean Region smallpox eradication advisers
November 1973	Pakistan	Pakistan and WHO Eastern Mediterranean Region smallpox eradication advisers
August 1974	India	Bangladesh, India and Nepal
January 1976	Nepal	6 countries of South-East Asia Region
March 1977	Kenya	4 countries of eastern Africa
September 1977	Kenya	5 countries of eastern Africa
April 1978	Kenya	5 countries of eastern Africa and the Eastern Mediterranean Region

[a] Participants included national programme staff and WHO smallpox advisers and other smallpox eradication staff from the regional offices and WHO Headquarters. Advisers from the regional offices in the 4 endemic regions were invited to all meetings from 1967 to 1970 and to the 1972 meeting in India.

Plate 10.15. Participants in the first interregional seminar on smallpox eradication held in Bangkok, Thailand, 11–16 December 1967. *Left to right, front row*: A. M. Khan (Pakistan), A. R. Rao (India), M. K. Singh (India), S. A. Mallick (Pakistan), D. A. Henderson (WHO), E. Na Bangxang (Thailand), S. Falkland (WHO), J. J. Dizon (Philippines), I. F. Setiady (Indonesia), U Thaung (Burma); *middle row*: Z. Rahman (Pakistan), C. Rubinstein (WHO), C. H. James (United Kingdom), J. Singh (Malaysia), K. S. Ramakrishnan (India), G. P. Nikolaevskij (WHO), W. H. Foege (USA), J. Keja (WHO), B. Ignjatovic (WHO), F. G. L. Gremliza (WHO), B. Wirjodipoero (Indonesia), J. C. Pitkin (WHO), Khin Mu Aye (WHO), K. Chatiyanonda (Thailand), S. Somachai (Thailand); *back row*: C. Patanacharoen (Thailand), A. Prajapati (Nepal), J. S. Copland (WHO), T. M. Mack (USA), G. H. Waheed (Afghanistan), B. Chantasut (Thailand), E. Shafa (WHO), R. M. Lyonnet (WHO), Y. K. Subrahmanyam (India), S. Singh (WHO), P. Tuchinda (Thailand), T. Phetsiriseng (Lao People's Democratic Republic), N. D. Tiep (Viet Nam), P. Kunasol (Thailand), C. Debyasuvarn (Thailand).

The meetings had both tangible and intangible benefits. Several specific changes in programmes can be associated with them: Indonesia's full commitment to smallpox eradication followed the 1967 meeting in Thailand; agreements to grant national surveillance and vaccination teams free passage across specified international borders, a hitherto unprecedented occurrence, followed the 1968 conference sponsored by CDC in Côte d'Ivoire and the 1973 meeting in Ethiopia; and India's decision to adopt the surveillance–containment strategy and to undertake an intensified programme followed the 1972 meeting in New Delhi.

Use of the Mass Media

The Smallpox Eradication unit staff actively sought publicity for the programme in national and international media, believing that it was important to make what was happening in the programme widely known to potential donors and to those in the endemic countries. For many sectors of government, this was a natural and logical approach but there was then, both in WHO and in many countries, a reluctance on the part of physicians and other health personnel to meet representatives of the mass media or to use the media except to convey traditional health education messages. The very small staff and limited programme of WHO's Division of Public Information at that time was a reflection of this attitude.

The publication of the semi-annual summaries of progress in smallpox eradication in the *Weekly epidemiological record* provided suitable occasions for press conferences, as did the occurrence of the last cases of smallpox in large countries and the certification of eradication in each of the countries and Regions. Efforts to obtain publicity were not without their embarrassing moments, however, the most awkward occurring on 14 October 1975, when Henderson, then on a visit to New York City, announced at a press conference that 8 weeks had elapsed since the last case of smallpox in Asia and, in view of the extent and effectiveness of surveillance, confidently stated that the last case of variola

major had been seen. Only 4 days later, however, another outbreak was found in Bangladesh (see Chapter 16).

As the programme progressed, increasing attention was given to contacts with the media (see Plate 10.16), particularly as the need for voluntary contributions became more urgent. Geneva was not so important a news centre as New York, in which there were more correspondents from many more countries. Fortunately, WHO maintained a small liaison office at the United Nations in New York with two public information officers, Ms Joan Bush and Mr Peter Ozorio, who were particularly effective in interesting the media in the programme. Among the unique ideas which they fostered were trans-atlantic press conferences, one in 1974, in which science writers and correspondents in New York and Washington interviewed Henderson in Geneva, and a second, in 1975, in which science writers in London and Dr Nicole Grasset, the adviser on smallpox eradication in the South-East Asia Region,

Plate 10.16. **A:** Lawrence K. Altman (b. 1937), correspondent for the *New York Times*, had been an epidemiologist with the measles control programme in western Africa in 1964–1965. **B:** James Magee (b. 1929) was the public information officer with the Smallpox Eradication unit, 1978–1980. **C** and **D:** Joan Bush (b. 1928) and Peter Ozorio (b. 1928) served in New York as public information officers attached to the WHO Liaison Office with the United Nations.

Libre de la Variole
La bataille contre la variole a été gagnée
DEATH OF A KILLER
Endlich frei
Als letzter Kontinent wurde nun auch Afrika
Feu la variole ?
Le mythe dangereux de l'éradication
Erradicada la viruela
天然痘、地球上から
科学と国際協力
Smallpox virus escapes in England; 'extinct' disease rears its ugly head
Vaccinations : l'antivariolique n'est plus obligatoire
mais les autres seront renforcées
Un triunfo de la OMS
La variole en Grande-Bretagne : pas de panique, recommande l'O.M.S.
Disease Has Killed Millions
WHO Ready to Declare Eradication of Smallpox
Un año sin un solo caso de viruela en el mundo
VARIOLE récompense de 100 000 F.D.
Doctor's World

Plate 10.17. A montage of newspaper articles published in 1978.

answered questions from New Delhi, India.

Especially extensive and helpful press coverage was provided twice during the programme—in 1974 and 1978. The first related to epidemic smallpox in India during 1974, the most critical year for smallpox eradication in Asia (see Chapters 15 and 16). In that year, a large number of correspondents, who had come to India to report on the detonation for the first time of an Indian

Publicizing the Programme

Special issues of the WHO magazine *World health*, stamps and medals served to publicize the programme and its accomplishments. In addition to the special issues of *World health* in 1965 on the theme "Smallpox: Constant Alert" and in 1975 on "Smallpox: Point of No Return", a third special issue was published in October 1972, with the slogan "Smallpox: Target Zero" (Plate 10.18). It coincided with the launching of what was termed the "final phase" which, at that time, was expected to result in eradication by the summer of 1974. As its introduction stated: "The global eradication programme this year, for the first time, extends into every state and province of every country where the disease exists. The final phase of the campaign is beginning." Unforeseen problems, however, resulted in the final phase lasting fully 3 years longer than had been optimistically envisaged.

World health featured the subject of smallpox on two other covers—in October 1979, on the occasion of certification of eradication in the last of the endemic countries, and in May 1980 (see Chapter 24, Plate 24.2), when the Thirty-third World Health Assembly accepted the recommendation of the Global Commission for the Certification of Smallpox Eradication that "smallpox eradication has been achieved throughout the world" and that "smallpox vaccination should be discontinued in every country except for investigators at special risk".

Postage stamps and cachets on the theme of smallpox eradication and vaccination were issued by many different governments between 1965 and 1980, as illustrated in Plates 10.19–10.22. The largest number were produced in 1978, the year after the world's last outbreak, in response to a recommendation by the Universal Postal Union to its member governments that smallpox eradication should be a principal philatelic theme. In 1978, too, the United Nations issued special stamps and silver medals in recognition of the achievement (Plate 10.23).

In some countries, stamps echoed the 1965 World Health Day theme of "Smallpox: Constant Alert"; several countries of western and central Africa issued stamps between 1968 and 1972 during the course of the programme for smallpox eradication and measles control, most of which featured pictures of the jet injector; and Guinea, on completion of its WHO-supported smallpox vaccine production laboratory, issued a full set of stamps depicting various stages in the vaccine production process (see Chapter 11, Plate 11.10).

In commemoration of the declaration at the Thirty-third World Health Assembly of the global eradication of smallpox, all delegations were presented with a set of medals as mementos (Plate 10.23); these bore inscriptions in the six official languages of WHO—Arabic, Chinese, English, French, Russian and Spanish.

nuclear device, discovered that the recorded incidence of smallpox was the highest for 20 years and reported this as well. Also in 1974, a series of articles published in the *New York Times* by Dr Lawrence Altman, who was on an extended tour of India and Bangladesh, vividly documented the magnitude of the effort being made and, in turn, stimulated the interest of other publications. The consequent international publicity brought greatly increased and badly needed support for the programme from senior government officials and played an important role in obtaining additional voluntary contributions. In 1978, world-wide press coverage followed the occurrence of 2 laboratory-associated smallpox cases in Birmingham, England (see Chapter 23) at a time when the Smallpox Eradication unit was having difficulties in persuading laboratories to destroy or transfer their stocks of variola virus. As a result, national governments took a special interest in the matter and compliance followed rapidly throughout the world.

As the goal of global eradication was approached, it was important for a quite different reason to publicize the status of smallpox and its anticipated demise. With the achievement of eradication, it would be possible to discontinue routine smallpox

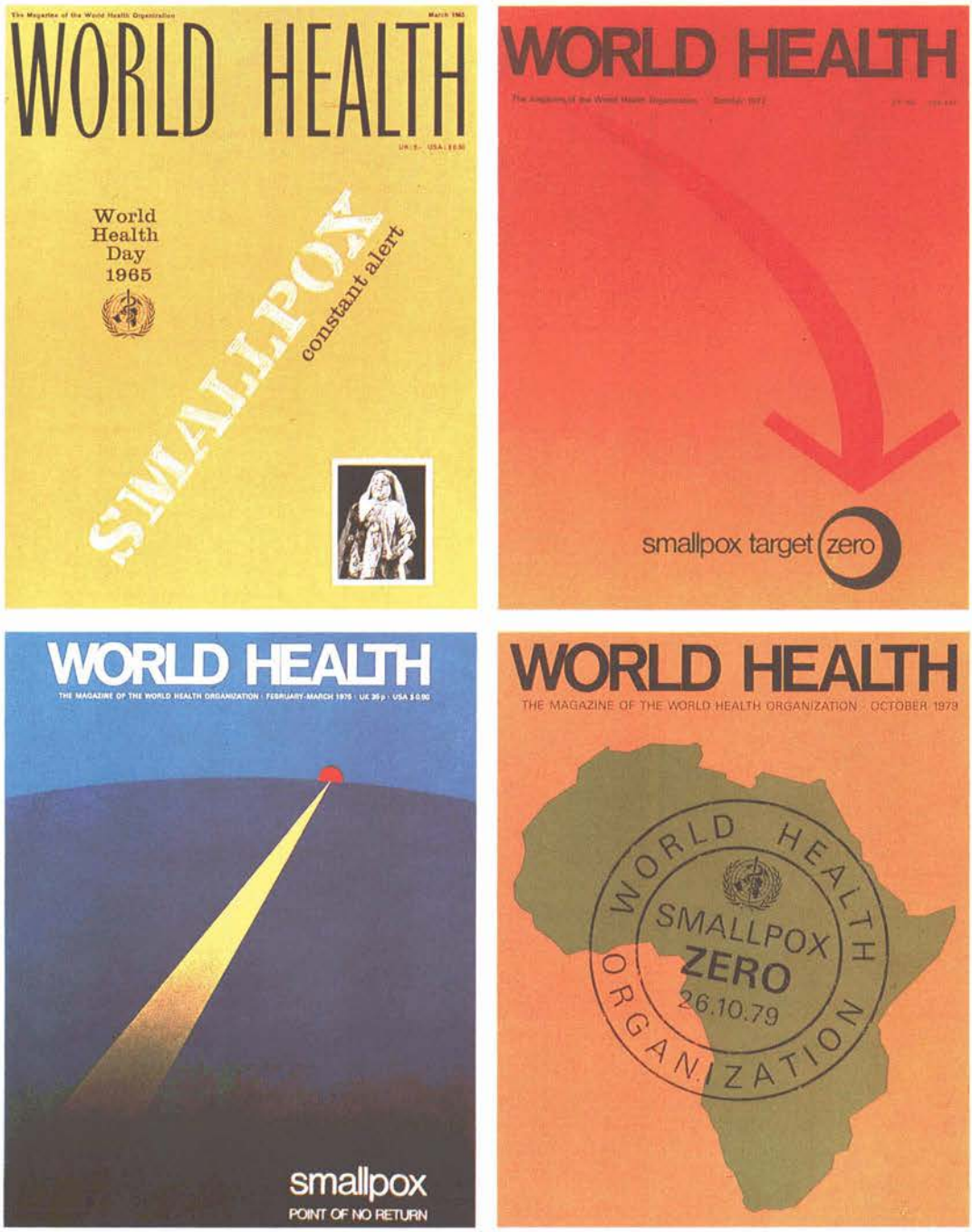


Plate 10.18. The smallpox eradication programme was presented in several issues of *World health*, an illustrated magazine published in many languages by WHO and directed to the general public.

Plate 10.19. Postage stamps depicting smallpox eradication activities issued by western and northern African countries between 1968 and 1975. The Libyan stamps at the lower right take up the theme of World Health Day, 7 April 1975: "Smallpox: Point of No Return".

Plate 10.20. Postage stamps issued in 1978 by Brazil, Egypt, Iraq, Ireland, Kuwait and Lesotho to celebrate the eradication of smallpox.

Plate 10.21. Postage stamps issued in 1978 by Malaysia, Maldives, Mozambique and Nigeria to celebrate the eradication of smallpox.

Plate 10.22. Postage stamps issued in 1978 by the Philippines, Senegal, Togo, Tunisia and the United Nations to celebrate the eradication of smallpox.

Plate 10.23. **A:** A proof set, presented to the Director-General of WHO by the United Nations, of sterling silver medals struck to celebrate the eradication of smallpox. The medals were issued on 31 March 1978 in the 5 original official languages of the United Nations in conjunction with the stamps shown in Plate 10.22. **B:** In May 1980, when the Thirty-third World Health Assembly had formally declared the global eradication of smallpox, each delegation to the Health Assembly received a set of commemorative medals in the 6 official languages of WHO.

vaccination as well as the use of international smallpox vaccination certificates. Vaccination was a long-established procedure, however, and it was unlikely to be discontinued unless both health officials and the public were aware of what had been accomplished and had confidence in that achievement. A public information officer, Mr James Magee, was therefore recruited to work full time with the Smallpox Eradication unit in Geneva.

Accounts of the progress made in the Intensified Programme appeared regularly in newspapers and magazines around the world, documentary films were made by the public broadcasting service in the USA and by Japanese television, and many countries issued special stamps; commemorative medals were also struck. Eventually, the press coverage became sufficiently extensive to cause one correspondent to write in *Science* (Wade, 1980) that "WHO has found numerous occasions on which to announce the eradication of smallpox. Another such announcement, issued with some new degree of bureaucratic solemnity, is due to emerge on 12 May. Experts consider that only definitive action by the Nobel Peace Prize committee can break the chain of transmission". However, despite numerous newspaper and magazine articles in countries throughout the world and in publications as diverse as *World health, National geographic, Reader's digest,* the *Encyclopaedia Britannica* and *Scientific American,* many persons of wide reading suggested to smallpox eradication staff that the achievement was too little known and that more should have been written about it.

INTERNATIONAL SUPPORT IN CASH AND IN KIND

One of the most difficult problems was that of ensuring adequate international support for the national programmes, whose needs changed, often substantially, from year to year. In the original plan presented by the Director-General to the Nineteenth World Health Assembly in 1966, four sources of support were envisaged: (1) the WHO regular budget which, in 1967, included US$2.4 million specifically earmarked for smallpox eradication; (2) contributions to the WHO Voluntary Fund for Health Promotion, Special Account for Smallpox Eradication, which the donor could make either in cash or in kind and which, if desired, could be assigned to a specific project or country; (3) bilateral contributions; and (4) contributions from other international agencies.

The Director-General's report to the Nineteenth World Health Assembly (World Health Organization, 1966b) had forecast a need for US$48.5 million in international assistance for a 10-year programme (1967–1976), of which one-third was expected to be provided by the WHO regular budget, the balance having to be obtained from the other sources. Ultimately, international assistance from 1967 to 1979, when eradication was certified, amounted to some US$98 million, of which US$34 million came from the WHO regular budget.

Of the expected sources of support, funds from the WHO regular budget were of particular importance because they could be used wherever required and for any appropriate purpose, including personnel and travel costs, the purchase of supplies and equipment, and local operational expenses—e.g., for petrol, vehicle repairs and living allowances for national staff. These funds served to complement voluntary contributions and national resources, which sometimes provided only partial support for a country programme. In programmes in western and central Africa, for example, national governments paid staff salaries and the USA provided all other needed resources except funds for the purchase of petrol and for vehicle repairs. Comparatively small sums from the WHO regular budget for "local costs", as they were termed, enabled governments in this region to undertake eradication programmes.

Undesignated gifts of cash to the WHO Special Account for Smallpox Eradication could likewise be used for any necessary purpose and had the further advantage that balances could be carried forward from year to year. Few undesignated gifts of cash were received, however, the contributions until 1974 being primarily in the form of vaccine. During the period 1974–1978, several donors made substantial cash contributions to the voluntary fund, almost all of which were designated for use in specific countries.

Significant bilateral support was provided by the USA and the USSR, the former providing almost all international assistance for programmes in western and central Africa, and the latter supplying very large quantities of vaccine to several Asian countries and to

some in Africa. International agencies other than WHO had been expected to provide substantial assistance but little was received.

Except for the first 2 years of the Intensified Programme (1967–1968), when activities in many countries were only just beginning, the inadequacy of resources presented a continuing problem. Headquarters, regional and national staff expended considerable time and effort in attempts to obtain assistance. Frequently, however, it was found that the available funds were sufficient to sustain activities for only a few months. The difficulties, even as late as 1975, may be illustrated by an estimate prepared in July of that year of the requirements and availability of resources for 1975 and the 2 subsequent years in addition to those provided under WHO's regular budget (Table 10.3).

Table 10.3. Estimated requirements and available resources as at July 1975, in addition to those provided under the WHO regular budget, 1975–1977 (US$)

Year	Amount needed	Available	Deficit
1975	1 975 000	1 445 000	530 000
1976	1 560 000	345 000	1 215 000
1977	1 450 000	345 000	1 105 000

It had been hoped that, when it became apparent that global eradication was feasible and perhaps within reach, funds would be more readily forthcoming. Even during 1976, however, with known smallpox confined to Ethiopia, the problem did not diminish, as is shown by a memorandum of 17 February 1976 from Henderson to the Director of the WHO Regional Office for the Eastern Mediterranean:

"I concur entirely with you in regard to your appraisal of need for a WHO epidemiologist to be attached to the smallpox eradication programmes in Sudan and Somalia ... I fear that there may be unknown foci ... which may yet cause real problems ... However, I'm very concerned about our funding position ... Frankly, at this time, we simply don't have the money to fund the Ethiopian programme beyond April or May and, at the same time, funds for Bangladesh will be exhausted at the end of March. One would have expected all sorts of support at this time but we are simply not getting it."

The WHO Regular Budget

Funds from the WHO regular budget were an important component of international assistance but it was difficult to apply them optimally in the context of ever-changing global needs. Their allocation by WHO Region and by country should ideally have taken into account both relative need and the global strategy, but this was difficult given WHO's decentralized structure and administrative procedures.

The WHO budget process was best suited to the support of a diverse array of national projects, which were usually small and had financial requirements that were reasonably predictable from year to year. The Director-General's annual budget, developed over a 2-year period, was a composite of proposals prepared separately by regional directors and Headquarters units and based, in part, on requests for assistance received from countries. Each regional director drew up a detailed budget specifying personnel and other costs for each project in each country and in the regional office. These project proposals were usually not reviewed by the relevant technical units at Headquarters, which similarly submitted detailed budget proposals of their own, broken down by permanent staff and consultant costs, as well as proposed expenditures for travel, meetings and other items. Following a review of the proposals by the Director-General and the assistant directors-general, an overall proposed programme and budget for the entire Organization was set out in detail for consideration by the Executive Board at its January session and by the World Health Assembly, which was usually convened in May—7 months before the beginning of the next financial year. The Smallpox Eradication unit had no indication as to the total allocations available for smallpox eradication each year until the budget volume was distributed.

The budget was almost invariably approved by the Health Assembly as presented, after which each regional director could transfer WHO regional resources from one project to another as need and opportunity presented. Funds could be transferred from one region to another only by the Director-General, but such transfers were seldom made.

In 1967, more than 90% of all the funds voted for smallpox eradication by the Health Assembly were allocated by the Director-General to the 4 regions in which endemic smallpox was then present (Table

10.4), only a small amount (about 8%) being provided to support Headquarters or interregional activities.

Because of the nature of the budget process, the Smallpox Eradication unit decided that the best way of achieving the optimum allocation of resources was through close collaborative planning with regional office staff. If this could be achieved, it was believed that a consensus on needs and priorities could be reached which would be reflected in annual budgets, and it would be possible to provide up-to-date information to regional directors so that transfers of funds could be made where required. Thus, each year, a planning meeting was scheduled which was attended by the officer responsible for smallpox eradication in each regional office together with senior Smallpox Eradication unit staff. Although it was usually possible to reach a consensus as to priorities and allocations of resources, the subsequent execution of agreed plans ranged from excellent to indifferent.

During the first 2 years of the Intensified Programme, the full utilization of appropriated funds was a major concern. At the Nineteenth World Health Assembly, in 1966, a number of delegates had proposed a budget of US$1 million for smallpox eradication, since they doubted whether the Organization could fully utilize US$2.4 million. Although the Director-General had assured them that the larger amount could be well used, this was, in fact, not easily accomplished. Before funds could be obligated, country plans and lists of the supplies and equipment needed had to be drawn up. With full-time advisers for smallpox eradication in only 2 of the WHO regions, and those not the most seriously affected, the task was not easy. Yet, if the funds were not fully expended, it would reflect poorly on the Organization. In 1967 and 1968, a lengthy correspondence was carried on with each of the WHO regions concerned, analysing and reanalysing budgets and obligations and repeatedly urging the regions to develop agreements and obligate funds as soon as possible.

The full obligation of allocated funds would have been facilitated by the procurement of a reserve fleet of vehicles, to be dispatched as they became needed by countries. This was a practice followed by UNICEF and one which would have alleviated serious delays in starting programmes, which were often caused by 12–18-month delivery times for vehicles. A proposal to this effect, however, was not accepted.

Table 10.4. Director-General's budgetary allocations for smallpox eradication for 1967 and estimated actual expenditure (US$)

Region	Budget allocations for smallpox	Estimated actual expenditure
Africa	658 428	460 090
Americas	629 000	742 063
South-East Asia	815 030	295 281
Europe	0	0
Eastern Mediterranean	246 706	573 999
Western Pacific	2 000	55 831
Headquarters and interregional	210 640	268 552
Total	2 561 804	2 395 816

In 1967, plans were quickly developed in the Region of the Americas and the Eastern Mediterranean Region but far less was accomplished in Africa and South-East Asia. As the year progressed, it became apparent that the funds committed in these latter regions would fall substantially short of those allocated. This problem, however, was solved in a manner that served indirectly to provide the Smallpox Eradication unit with added discretionary resources for emergency needs. Towards the end of 1967, the Regional Director for South-East Asia was persuaded to release funds allocated for use elsewhere and the Director-General approved the transfer. Some were transferred to the Regions of the Americas and the Eastern Mediterranean and some were used for the purchase of large numbers of the new bifurcated needles and jet injectors. The subsequent ability to dispatch bifurcated needles and jet injectors (as well as vaccine) promptly to countries in need was of great help in carrying out programme activities. The Regional Director for Africa chose not to release his unobligated funds and, in December, at the end of the financial year, they were returned to Headquarters. Fortunately, however, it proved possible to recover them for the programme, thanks to the Division of Budget and Finance. Cash contributions to the WHO Voluntary Fund for Health Promotion's Special Account for Smallpox Eradication had not been large, but a moderate sum had accumulated by 1967. In that year, virtually all these funds had been spent on travel, consultants and training materials. The unobligated funds from the African Region were used to cover these

expenditures, and the cash balance in the special account was restored and carried forward to the following year. Almost every year thereafter unobligated funds from the regions enabled the cash balance in the special account to be largely restored, thus providing a small but immensely valuable cash reserve to supplement the meagre discretionary funds otherwise available for smallpox eradication through Headquarters accounts.

By 1969, most countries had begun eradication programmes and the problem of lack of funds replaced that of utilizing budgeted allocations. As Henderson wrote to the regional smallpox adviser in the Americas (21 February 1969):

"I am concerned about the problem of money this year for I am afraid we will be very hard pressed indeed. We could use substantially more in the African Region; the Eastern Mediterranean Region has requested some additional [funds] ... and the South-East Asia Region, if the Indian programme accelerates as expected, could use everything we have. I am afraid the honeymoon is over with respect to finances."

It was also pointed out that Brazil, the only endemic country in the Region of the Americas, had already received substantial resources, including funds released in 1967 by the South-East Asia Region, and it was suggested that the Region of the Americas might reciprocate by releasing some of its funds for use elsewhere. However, such transfers of funds were not customary and this proposal was rejected, as were similar subsequent ones.

To achieve a more appropriate distribution of funds, the next best approach seemed to be to attempt to change the regional allocations from year to year to reflect more accurately the relative balance of needs in the different regions. The first allocations, in 1967, had necessarily been arbitrary ones, since it had not been possible at that time to make accurate estimates of need by region. Up to 1970, the allocations remained essentially unchanged but, by then, it was increasingly apparent that far less would be required in the Americas during future years but far more in Asia and Africa and that a reapportionment based on longer-term requirements was needed. Throughout 1970, Smallpox Eradication unit staff worked closely with those in the regions to reach a consensus on future needs. Towards the end of the year, however, the unit was informed that proposals based on these analyses would not be approved by the Director-General. Although the exercise had proved futile, it was hoped that it might still be possible at least to reduce the allocation to the Americas and to increase it in other regions. In a memorandum (dated 30 December 1970) to his Assistant Director-General, Henderson pointed out:

"Plentiful funds are available in the Region of the Americas as confirmed in discussions in Washington during December ... all concerned feel confident that smallpox transmission in the Americas will be interrupted in 1971. It is proposed that smallpox eradication funds be used to strengthen surveillance activities [in the Americas] ... However, even if gilt-edged support is provided to this enterprise, it is agreed that it would be difficult to expend more than $250–300 000 per year [of a budgeted US$569 000]."

The proposed change in allocation was discussed with the Regional Director for the Americas, who agreed with the budget analysis but pointed out that he needed more funds for malaria eradication and asked for some sort of trade-off so as to maintain his regional budget at a more constant level. The Director-General decided, however, not to alter the regional allocations for smallpox eradication for 1971 and, from 1972, the practice of identifying a specific allocation for smallpox eradication was discontinued. This ended the efforts to develop plans for the better deployment of funds from WHO's regular budget. After 1971, it was no longer required that a prescribed minimum amount should be spent on smallpox eradication; the regional directors allocated funds from their overall allotments on the basis of their sense of the programme's priority in relation to the other needs in their regions.

When inflation is taken into account, as was customary each year in preparing WHO's overall budget, the Organization's annual expenditures for the programme up to 1976 were close to the appropriation of US$2.4 million originally approved by the Health Assembly in 1966 (Table 10.5). However, as the number of endemic countries decreased, increasing problems were encountered in obtaining the support necessary to complete the programme and to permit certification, as is shown by a memorandum of 6 January 1975 from Henderson to the Director-General:

"We may face some difficult questions at the Executive Board in regard to the smallpox budget

which we should be prepared for. In November, a special appeal was made by the Director-General for additional funds for the smallpox programme. The importance of the programme and the high priority given to it by the Organization was emphasized. Only $2.1 million of the $3.3 million requested has so far been received but we know of at least five additional countries which have indicated that additional support might be forthcoming.

"The difficult problem about which questions will almost certainly be forthcoming is why the Organization cut the smallpox allocations (by 29%) if it accords the programme such high priority and is asking for special donations. The budget cuts are evident not only in the Regions but also at Headquarters.

"As the first knowledge which I had in regard to the budget levels was when I received Official Records No. 220 [Proposed Programme and Budget for 1976–1977], I find it difficult to contrive a suitable answer which might be proposed. And yet, an inappropriate response could be most damaging, as I'm sure you would agree."

Questions were asked by the Board but the budget was not changed.

Other Types of Assistance to Programmes

As has been mentioned earlier, it was expected that two-thirds of the total costs of the smallpox eradication programme would be met by international agencies other than WHO and by voluntary contributions to governments or to the Special Account for Smallpox Eradication in the WHO Voluntary Fund for Health Promotion. In view of the level of support for smallpox eradication during 1959–1966 (see Chapter 9), this originally seemed to be an unrealistic expectation, but such contributions eventually amounted to US$66.9 million over the period 1967–1979 (Table 10.6).

The different types of contribution are, for the most part, considered together in this section, since it is somewhat arbitrary to identify some as bilateral contributions, some as support to the Special Account for Smallpox Eradication and some as contributions by other international organizations. For example, the substantial cash contributions made by Denmark, Norway and Sweden to programmes in Bangladesh and India during 1974–1977 were provided through the special account for administrative convenience but were a part of the bilateral assistance funds already allocated for use in these countries. Similarly, support from two United Nations organs, the United Nations Emergency Operation (UNEO) in Bangladesh in 1972 and the Office of the United Nations Disaster Relief Co-ordinator (UNDRO) in Somalia in 1977, consisted of supplies and equipment provided by national governments in response to emergency appeals rather than of funds from the established budgets of these organs.

Throughout the programme, an effort was made to account for and place a cash value on the support provided by different agencies. The data as presented, however, suggest a greater precision and completeness in accounting than is, in fact, the case. Many of the contributions were in kind rather than in cash. When a contribution was provided through the Voluntary Fund for Health Promotion, the donor was responsible for

Table 10.5. Expenditure on smallpox eradication from the WHO regular budget in real and constant dollars, 1967–1979 (US$)

Year	Headquarters	Interregional	African Region	Region of the Americas	South-East Asia Region	Eastern Mediterranean Region	Western Pacific Region	Total (US$)	Total in terms of 1967 US$
1967	157 076	111 476	460 090	742 063	295 281	573 999	55 831	2 395 816	2 395 816
1968	180 086	102 511	722 141	815 574	555 634	348 886	3 940	2 728 772	2 647 209
1969	177 966	163 498	951 237	669 142	273 406	649 938	4 491	2 889 678	2 716 933
1970	217 060	83 153	919 020	579 164	460 709	722 587	6 208	2 987 901	2 719 976
1971	219 047	123 574	942 962	503 408	573 279	702 999	4 767	3 070 036	2 652 910
1972	240 460	137 430	1 000 040	481 819	787 081	654 801	2 858	3 304 489	2 702 841
1973	308 490	235 606	694 770	191 259	1 002 489	735 975	0	3 168 589	2 445 327
1974	281 440	273 912	278 599	143 831	1 110 656	960 030	2 838	3 051 306	2 213 845
1975	292 089	406 083	156 130	117 687	1 546 243	540 669	0	3 060 901	2 079 423
1976	480 037	988 866	110 323	0	601 825	1 366 648	0	3 547 699	2 265 525
1977	415 112	1 137 518	26 048	0	439 507	163 130	0	2 181 315	1 304 056
1978	310	504 200	6 944	0	114 646	109 872	0	735 972	409 988
1979	0	344 855	0	0	67 777	30 142	0	442 774	228 604
Total	2 969 173	4 614 682	6 268 304	4 243 947	7 828 533	7 559 676	80 933	33 565 248	26 782 452

Table 10.6. Contributions for smallpox eradication in cash or in kind to the WHO Voluntary Fund for Health Promotion, Special Account for Smallpox Eradication, and from sources of bilateral support, 1967–1979 (US$)

Contributor	Total	Voluntary Fund for Health Promotion, Special Account for Smallpox Eradication		Bilateral support (cash and kind)
		Cash	Kind	
Australia	33 625	33 625	–	0
Austria	75 500	5 000	–	70 500
Argentina	13 275	–	13 275	0
Belgium	378 800	–	378 800	0
Brazil	128 925	–	128 925	0
Cameroon	707	707	–	0
Canada	2 505 061	1 306 779	1 156 282	42 000
Colombia	3 002	–	3 002	0
Czechoslovakia	41 118	–	41 118	0
Denmark	1 083 062	1 083 062	–	0
Finland	110 623	19 663	90 960	0
German Democratic Republic	26 417	–	26 417	0
Germany, Federal Republic of	503 767	127 004	–	376 763
Ghana	3 273	3 273	–	0
Greece	23 000	23 000	–	0
Guinea	18 529	–	18 529	0
Hungary	33 500	–	33 500	0
India	503 691	–	207 291	296 400
Iran	874 000	500 000	374 000	0
Japan	634 198	268 400	223 598	142 200
Jordan	140	–	140	0
Kenya	168 000	–	168 000	0
Kuwait	12 992	12 992	–	0
Luxembourg	6 541	6 541	–	0
Monaco	2 419	–	2 419	0
Netherlands	2 803 133	2 613 393	177 870	11 870
New Zealand	10 500	–	10 500	0
Nigeria	16 036	16 036	–	0
Norway	998 530	998 530	–	0
Peru	3 000	–	3 000	0
Philippines	5 000	–	5 000	0
Poland	3 500	–	3 500	0
Saudi Arabia	200 000	200 000	–	0
Sweden	15 689 584	15 408 504	281 080	0
Switzerland	372 169	118 659	219 910	33 600
Thailand	3 565	–	3 565	0
Uganda	12 077	12 077	–	0
Union of Soviet Socialist Republics	8 805 610	–	3 531 913	5 273 697
United Kingdom	1 020 924	1 010 924	–	10 000
United States of America	24 974 003	6 339 900	1 258 408	17 375 695
Yugoslavia	26 000	–	26 000	0
Zaire	2 500	2 500	–	0
Council of Arab Ministers' Fund for Health Development	20 350	–	20 350	0
Japan Shipbuilding Industry Foundation	1 769 344	1 769 344	–	0
OXFAM	103 104	3 104	–	100 000
Tata Iron & Steel Co. Ltd (India)	536 399	–	–	536 399
Other	52 238	26 806	25 432	0
Subtotal	64 611 731	31 909 823	8 432 784	24 269 124
UNDP (United Nations Development Programme)	299 344	–	–	299 344
UNDRO (Office of the United Nations Disaster Relief Coordinator)	470 849	–	–	470 849
UNEO (United Nations Emergency Operation)	750 000	–	–	750 000
UNICEF (United Nations Children's Fund)	427 878	–	–	427 878
UNROD (United Nations Relief Operation, Dacca)	415 500	–	–	415 500
Subtotal	2 363 571	–	–	2 363 571
Total	66 975 302	31 909 823	8 432 784	26 632 695

assigning a cash value to it but different donors assigned different values to the same product. For example, most vaccine was valued at US$10–16 per 1000 doses but values as high as US$256 per 1000 doses were assigned by some donors. The average value for all vaccine contributed worked out at US$17 per 1000 doses, although estimates of the actual costs of vaccine production in the industrialized countries in the early 1970s were in the range of US$30–40 per 1000 doses.

It may be noted that in several instances the amounts in Table 10.6 are different from those recorded by the Global Commission for the Certification of Smallpox Eradication in Annex 16 to its Final Report (World Health Organization, 1980). The differences are the consequences of adjustments made in the light of more recent information. In addition, Annex 16 included the value of some bilateral contributions made before 1967 (notably by the USA and the USSR) and of cash and vaccine pledged during the period 1967–1979 by India, the USSR and the Japan Shipbuilding Industry Foundation but received after 1979; these amounts have been omitted from Table 10.6.

An attempt was also made to place a cash value on the services of volunteer personnel. For accounting purposes, a figure of US$750 per month was assigned, an estimate provided by one of the principal donor governments. This figure, as well as a number of other approximations that were made, undoubtedly understates to some degree the value of gifts in kind. All but impossible to estimate, and not included here, is the value of services provided by many local, non-governmental groups, such as the League of Red Cross and Red Crescent Societies; Kiwanis, Lions and Rotary Clubs; youth groups, such as the Boy Scouts and Girl Guides; and missionary groups. In a number of countries such groups were most helpful in organizing vaccination campaigns, mobilizing public support and, sometimes, performing vaccinations. A few contributed funds in support of local programmes, although in comparison with national and international contributions, the cash value of all such contributions was not large.

Although voluntary contributions were recognized by the Health Assembly to be an essential adjunct to the WHO regular budget, such support was difficult to obtain. Every year, Health Assembly resolutions requested all countries to provide additional support and every year the Director-General sent letters to all Member States and to relevant international agencies, referring to the Health Assembly resolution and asking for help. Smallpox eradication programme staff regularly met potential donors at the World Health Assembly and during special visits to national capitals and embassies; special meetings of potential donors were convened; and influential national figures who were sympathetic to the programme were regularly contacted to seek their good offices in obtaining support. Despite these efforts and despite the fact that the eradication of smallpox would be of great benefit to all countries, contributions were modest at best. This may have reflected a certain scepticism as to the feasibility of eradication; however, it also reflected the fact that WHO, except for malaria eradication, had not previously been active in seeking supplementary contributions and governments were unaccustomed to making them. As Table 10.7 shows, except in respect of malaria eradication, the contributions to the special accounts that made up the Voluntary Fund for Health Promotion did not exceed US$2 million in any year until 1968, and of all the contributions made between 1967 and 1975, 18% were for smallpox eradication.

Vaccine for the programme was obtained entirely from voluntary contributions or local production. From 1967 to 1979, 27 countries contributed 407 million doses of vaccine to the Voluntary Fund, more than 60% of this coming from the USSR. Although industrialized countries provided most of the donated vaccine, notable contributions of vaccine were also made by Argentina, Brazil, Colombia, Guinea, India, Iran, Kenya, Peru, Philippines and Thailand.

Efforts to obtain support from UNICEF and the United Nations Development Programme (UNDP) proved disappointing, although both agencies had previously given significant support to other WHO programmes, as well as some support for smallpox eradication before 1967. Between 1967 and 1972, UNICEF provided US$427 878 for vaccine and vaccine production equipment but none thereafter—a policy reflecting its disappointment with the lack of progress in malaria eradication and its decision not to support another attempt to eradicate a disease. The possibility of support from UNDP was explored with the resident

Table 10.7. Contributions in cash or in kind to the WHO Voluntary Fund for Health Promotion or to special accounts,[a] by year, 1956–1979 (US$)[b]

Year	Malaria eradication	Smallpox eradication	Other	Total
1956	68 096	–	–	68 096
1957	5 046 909	–	–	5 046 909
1958	169 506	285 000	300 000	754 506
1959	6 284 766	–	500 000	6 784 766
1960	1 202 317	104 010	622 488	1 928 815
1961	4 464 094	96 000	1 266 674	5 826 768
1962	590 437	3 800	573 115	1 167 352
1963	2 718 815	5 060	1 572 479	4 296 354
1964	163 300	316 694	1 148 857	1 628 851
1965	86 890	24 936	843 843	955 669
1966	77 225	40 780	1 449 518	1 567 523
1967	37 050	202 305	611 747	851 102
1968	46 711	313 233	2 233 294	2 593 238
1969	36 854	239 457	1 408 438	1 684 749
1970	52 977	337 820	2 352 518	2 743 315
1971	85 339	810 708	5 957 930	6 853 977
1972	157 009	780 632	4 368 568	5 306 209
1973	252 392	1 288 137	10 683 838	12 224 367
1974	257 823	4 533 310	11 032 822	15 823 955
1975	1 307 009	10 522 835	20 535 705	32 365 549
1976	388 367	9 448 523	22 393 979	32 230 869
1977	973 150	5 272 392	28 886 320	35 131 862
1978	7 134 651	5 690 337	35 129 741	47 954 729
1979	2 117 617	902 918	29 101 543	32 122 078
Total	33 719 304	41 218 887	182 973 417	257 911 608

[a] Special accounts were amalgamated, as sub-accounts, into the Voluntary Fund for Health Promotion when that was established by the World Health Assembly in 1960 (except for the Malaria Eradication Special Account, which was placed in the Voluntary Fund in 1964).

[b] Excludes income from interest, revenue from sales, and savings.

representatives in several countries, but lack of interest, the complexities involved in developing suitable proposals and the delays in securing their approval restricted support to US$299 344.

Between 1967 and 1970, over half of all international expenditure on smallpox eradication was met by bilateral contributions (Table 10.8), representing primarily United States support for the programme in western and central Africa and contributions of vaccine by the USSR to India and several smaller Asian countries. With the achievement of smallpox eradication in western and central Africa in 1970, support for that programme began to be phased out and India, during the early 1970s, began to rely increasingly on domestically produced vaccine. Bilateral contributions diminished proportionately, and after 1972 exceeded US$1 000 000 only in 1974 and 1975.

Expenditure from the Special Account for Smallpox Eradication up to the end of 1973 was accounted for primarily by the distribution of donated vaccine. The amounts increased steadily over the years, reaching US$845 150 in 1973. Two-thirds of the expenditure on smallpox eradication in 1973, however, were met by WHO's regular budget.

Contributions to the Voluntary Fund increased significantly from 1974 onwards. In the autumn of 1973, smallpox eradication activities had been intensified in Asia, but the problems encountered in India proved far more formidable than had been anticipated (see Chapter 15) and, in response to special appeals for assistance, Sweden began to contribute substantial sums to the Voluntary Fund for use in that country, amounting in total to more than US$9 million during 1974–1976. As difficulties mounted in Bangladesh as well, Sweden, and later Norway and Denmark, joined together to provide more than US$5 million for its programme. Substantial additional assistance for India was also provided by the Tata Iron and Steel Company of India, by Iran and by OXFAM.

In 1974, it was also possible to intensify the programme in Ethiopia, the only endemic country outside Asia, thanks to support from the United States Public Health Service, which began to make funds available for leasing helicopters, nearly US$2 million being provided for this purpose from 1974 to 1977. AID contributed US$3 million to the Voluntary Fund in 1976–1977 in support of the Ethiopian programme and additional assistance was provided by Australia, Austria, Finland, the Federal Republic of Germany and Japan. Finally, with the reintroduction of smallpox into Somalia in 1976 (see Chapter 22), special appeals for funds brought contributions from the USA and from UNDRO. Meanwhile, cash contributions which could be used wherever required were provided by Canada, the Netherlands, the United Kingdom, Switzerland and the Japan Shipbuilding Industry Foundation.

By 1977, the year in which the last endemic case occurred, the Voluntary Fund covered more than 70% of all expenditures; during the period of certification activities, 1978–1979, WHO regular budget allocations were sharply decreased and the coverage by the Voluntary Fund increased to 80–90%.

Although the increase in voluntary contributions from 1974 onwards coincided with a growing recognition of the feasibility of global smallpox eradication, the donations proved to be almost as difficult to obtain as in

earlier years. A review of the origin and history of each of the contributions shows that personal, often repeated, appeals by individual members of the smallpox eradication programme staff had to be made in order to obtain each contribution.

SUPPLY OF VACCINE AND VACCINATION INSTRUMENTS

The availability at all times of satisfactory freeze-dried vaccine and vaccination instruments was essential to the successful execution of the programme. Without vaccine and bifurcated needles or jet injectors, programme staff could do nothing; with them, methods could usually be devised to deal, at least to some extent, with shortages of transport and equipment, and so sustain both momentum and morale. Because of the importance of vaccine and vaccination instruments, Chapter 11 is devoted exclusively to the subject. Here, we summarize the methods used to ensure that both were readily available to all endemic countries and to those adjacent to them.

Vaccine Requirements

It had originally, but erroneously, been assumed that the provision of adequate quantities of suitable freeze-dried vaccine would not present a major problem. It was believed that, for most endemic countries, if sufficient vaccine were not already available, it would either be provided in the form of bilateral contributions or soon be produced in the endemic countries themselves. Additional requirements would be met through contributions made through the Voluntary Fund for Health Promotion, the pledged annual contribution of 25 million doses by the USSR being considered almost sufficient for this purpose.

From what was known in 1967, adequate supplies of vaccine appeared to be available. In the Americas a number of laboratories were already producing freeze-dried vaccine and an agreement was signed by the Pan American Health Organization with Connaught Laboratories of Canada to provide for continuing consultation, the training of technicians and the monitoring of vaccine throughout that region. It seemed, therefore, that this region was already self-sufficient, or soon would be. In the African Region, the programme in western and central Africa was being carried out with the assistance of the USA, which provided the necessary vaccine to 20 countries. In virtually all other countries, some type of vaccination programme was in progress and it was assumed that many had already obtained satisfactory vaccine from some source, although it was recognized that additional vaccine would be required if the programmes were to be intensified. In the South-East Asia Region, only Nepal and possibly Indonesia among the endemic countries appeared to require vaccine. India's needs were being met by domestic production and bilateral contributions from the USSR.

Table 10.8. International expenditure on smallpox eradication, 1967–1979 (US$)

Year	WHO regular budget	Voluntary Fund for Health Promotion, Special Account for Smallpox Eradication	Other organs of United Nations system	Bilateral support	Total
1967	2 395 816	194 889	526 476	3 911 700	7 028 881
1968	2 728 772	255 927	116 774	4 163 680	7 265 153
1969	2 889 678	233 635	83 713	4 334 060	7 541 086
1970	2 987 901	375 434	61 644	3 918 307	7 343 286
1971	3 070 036	608 403	34 772	2 377 650	6 090 861
1972	3 304 489	727 581	448 100	1 397 627	5 877 797
1973	3 168 589	845 150	–	997 655	5 011 394
1974	3 051 306	3 127 169	–	1 086 907	7 265 382
1975	3 060 901	8 065 031	631 696	1 494 282	13 251 910
1976	3 547 699	6 629 430	118 304	189 313	10 484 746
1977	2 181 315	6 724 347	470 849	9 780	9 386 291
1978	735 972	4 364 812	–	388 163	5 488 947
1979	442 774	5 491 229	–	–	5 934 003
Total	33 565 248	37 643 037	2 492 328	24 269 124	97 969 737

Afghanistan and Burma were also receiving vaccine from the USSR. In the Eastern Mediterranean Region, Pakistan was thought to be producing sufficient vaccine for its own needs in a laboratory in Dhaka, and the quantities required for Ethiopia, Somalia, the Sudan and Yemen were thought not to be great.

In 1967, a detailed survey of the amount and quality of vaccine being produced throughout the world revealed that the situation was much less satisfactory than had been thought. It was discovered that much of the vaccine then in use was produced by laboratories which did not test it for stability, while some laboratories determined potency simply by vaccinating a group of young children. When tested by the 2 WHO reference laboratories, much of the vaccine from developing countries and some from industrialized ones did not meet the international standards.

During the first 2–3 years of the Intensified Programme, the provision of vaccine was not a major problem, however, because of the time required for national programmes to organize activities aimed at increasing substantially the number of vaccinations performed. Of the countries in which major programmes began in 1967, Brazil produced sufficient vaccine for its own needs and, as has already been mentioned, the countries of western and central Africa were supplied by the USA. To ensure an adequate supply of vaccine of proven potency to meet the needs of other countries, a number of measures had to be taken quickly: (1) vaccine production laboratories in endemic countries were supported by the provision of consultants, equipment and production manuals; (2) the WHO reference laboratories agreed to test all batches of vaccine produced by newly established laboratories and to participate in research and other activities which would enhance and/or simplify production methods; (3) a system of international quality control was established for all vaccine used in the Intensified Programme, whether locally produced or donated through bilateral assistance or by WHO; (4) vaccination devices were tested and introduced which used less vaccine than conventional techniques; and (5) additional contributions of vaccine were sought. As a result, sufficient vaccine of adequate quality was eventually ensured for every endemic country, although for many years reserve supplies remained perilously low.

Plate 10.24. Ryoichi Sasakawa, President of the Japan Shipbuilding Industry Foundation, presents a cheque for US$500 000 to F. J. Dy, Director of the WHO Regional Office for the Western Pacific in November 1975. Masami Tanaka, Minister of Public Health of Japan, stands between them. The Foundation later increased its support to WHO for smallpox eradication to a total of nearly US$1.8 million, the largest amount given by a nongovernmental organization.

Support for Production Laboratories in Endemic Countries

Of the commonly used vaccines, smallpox vaccine was the easiest to produce and laboratories already existed in a number of developing countries. Priority was given to the support of laboratories in the countries with the largest populations in order both to improve the quality of their vaccine and to increase their capacity, in the expectation that voluntary contributions would meet the needs of others. A first step was to simplify and standardize production methods. The principles on which vaccine production was based were similar throughout the world, but techniques differed widely from one laboratory to another. In 1968, therefore, a meeting of the most experienced vaccine producers was convened to develop a manual (SE/68.3 Rev.2) which described in detail the optimum production procedures. Selected consultants then repeatedly visited laboratories in the endemic countries to help them to improve methods and expand capacity. On the basis of their recommendations, additional equipment and supplies were provided. Vials of seed virus for use in production, as well as

reference specimens for testing, were prepared and distributed by the National Institute of Public Health, Bilthoven, Netherlands; when the laboratories began production, batches of vaccine were tested by one or the other of the two WHO reference laboratories.

Year by year, the quantity of vaccine produced in the developing countries increased and its quality improved. In the South-East Asia Region, Burma became self-sufficient in 1969 and Indonesia in 1970; India's 4 laboratories slowly but steadily increased the quantity and quality of their vaccine. The laboratory in Dhaka likewise increased production to provide sufficient vaccine for East Pakistan, although some additional supply had to be provided during the intensified programme in 1973–1975, in what was then Bangladesh. In the African Region, support was provided to laboratories in Guinea, Kenya and Nigeria in the hope that they might serve as producers for large regions of eastern and western Africa. Kenya, by late 1968, was able to produce sufficient vaccine for several countries in eastern Africa; the laboratory in Guinea took much longer to begin production and never succeeded in producing large quantities; the laboratory in Nigeria produced only a few satisfactory experimental batches. In the Americas, most of the countries conducting programmes quickly became self-sufficient and contributed vaccine to others requiring it. Brazil, as noted above, produced sufficient vaccine for its own needs and, although many batches did not meet international standards, especially for stability, the vaccine was effective provided that it was kept cold until the time of application. The Eastern Mediterranean Region was ultimately to require the largest amounts of vaccine. Efforts to establish a laboratory in Pakistan, the country with the largest population in the region, failed because of national administrative problems, but by 1973 sufficient vaccine to meet most of Pakistan's needs was being provided by Iran. Assistance was also given to laboratories in Ethiopia, Iraq and the Syrian Arab Republic, but none of these succeeded in producing more than small quantities of satisfactory freeze-dried vaccine.

By 1971, approximately 250 million doses of vaccine were being produced annually in the endemic regions, and by then all the vaccine used in national programmes, except in Brazil, met international standards.

Vaccine Donations

Most of the contributed vaccine was provided under bilateral agreements by the USSR, which donated more than 1400 million doses from 1958 to 1979. The USA provided more than 190 million doses, primarily to the western and central African countries, also under bilateral agreements. Contributions from other countries usually amounted to no more than a few million doses each year (see Chapter 11, Table 11.15 for the quantities contributed to WHO between 1967 and 1984). In part, this was because most industrialized countries produced their own vaccines in small national or quasi-national laboratories. Most produced little or no freeze-dried vaccine, preferring instead the glycerolated liquid vaccine, which could be dispensed more conveniently in single-dose capillaries. Although the vaccine had to be kept constantly under refrigeration, this caused little difficulty for the industrialized countries.

Except for the vaccine provided under bilateral agreements by the USSR and the USA, virtually all vaccine contributions were made through the WHO Voluntary Fund for Health Promotion. Until 1967, arranging for the acceptance and shipment of vaccine contributed to WHO was complicated and time-consuming, usually requiring 6–18 months (see Chapters 9 and 11). Several measures were therefore taken to reduce the processing interval to only 6–8 weeks. The Smallpox Eradication unit assumed responsibility for arranging for tests of batches of vaccine proposed for donation and the National Institute of Public Health, Bilthoven, agreed to examine specimens as soon as received. Specimens were shipped promptly and the results reported by telex or telephone. One obstacle to rapid processing was the requirement that vaccine titres should be determined after incubation for 4 weeks at 37 °C. When it was shown in 1969 that all vaccine batches with an adequate titre after incubation for 1 hour at 100 °C also met conventional stability tests (Arita, 1973), it was possible further to reduce the time required for testing by 4 weeks. Another problem had been that of arranging for the prompt shipment of vaccine from donor laboratory to recipient country. Many donors waited until vaccine was requested before beginning production but, even when it was available in stock, many delays occurred in arranging for international shipment. WHO

Table 10.9. Quantities of vaccine supplied annually from vaccine donated to WHO (thousands of conventional doses)[a]

Country or organization	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	Total
Africa														
Benin	0	0	0	0	0	0	0	2	0	0	0	672	0	674
Botswana	0	0	0	0	245	445	100	190	194	256	292	220	237	2 179
Burundi	1 000	200	0	725	758	315	0	250	0	177	0	64	0	3 489
Cameroon	0	0	0	0	0	0	300	0	0	0	830	0	0	1 130
Cape Verde	0	0	0	0	0	0	0	0	155	80	64	6	32	337
Central African Republic	0	0	0	0	0	0	120	0	0	0	0	224	0	344
Chad	0	0	0	0	0	0	300	0	0	0	0	360	0	660
Comoros	0	0	0	0	0	0	0	0	0	120	100	0	0	220
Congo	0	0	0	0	0	0	190	10	0	0	0	496	0	696
Djibouti	0	0	0	0	0	0	0	0	0	0	0	100	0	100
Equatorial Guinea	0	0	17	0	0	0	0	0	0	0	64	0	0	81
Ethiopia	0	0	0	315	4 323	2 432	1 998	2 468	2 384	5 720	3 048	560	25	23 273
Gabon	0	0	0	0	0	100	65	0	0	0	0	0	0	165
Gambia	0	0	0	0	0	0	0	0	0	0	46	32	0	78
Ghana	0	0	0	0	0	0	0	22	0	10	18	0	0	50
Guinea	749	0	0	0	0	0	0	0	0	0	0	0	0	749
Guinea-Bissau	0	0	0	0	0	0	0	0	100	0	0	0	0	100
Lesotho	0	0	0	210	70	105	20	0	40	90	152	48	96	831
Liberia	250	0	0	0	0	0	20	0	0	0	0	128	0	398
Malawi	0	508	300	1 007	525	1 000	500	1 007	953	500	610	600	315	7 825
Mali	100	0	0	0	0	0	810	295	0	0	0	320	0	1 525
Mauritania	0	0	0	0	0	90	260	107	80	0	64	224	0	825
Mauritius	0	100	158	35	105	70	105	35	32	32	35	32	37	776
Mozambique	0	0	0	0	0	0	0	0	0	848	1 824	1 968	375	5 015
Niger	0	0	0	0	0	0	0	0	0	675	0	0	0	675
Nigeria	0	0	0	0	0	0	2 010	0	0	0	0	0	0	2 010
Rwanda	0	0	1 050	500	0	112	205	280	204	211	198	536	0	3 296
Sao Tome and Principe	0	0	0	0	0	0	0	0	0	20	0	6	20	46
Sierra Leone	550	250	0	0	0	0	0	0	0	0	0	60	0	860
Somalia	66	30	35	370	105	623	624	650	608	1 151	3 904	1 524	0	9 690
Sudan	2 010	3 658	2 490	3 500	244	1 990	1 485	490	512	256	640	416	542	18 233
Swaziland	0	0	0	0	0	0	80	47	0	100	69	64	64	424
Togo	0	0	0	0	0	0	125	0	0	0	0	0	0	125
Tunisia	0	0	0	210	1 085	560	1 110	600	256	0	0	0	0	3 821
Uganda	0	800	1 100	2 850	1 000	495	500	510	501	263	240	256	0	8 515
United Republic of Tanzania	1 014	0	2 500	2 000	1 990	968	820	1 984	1 017	550	2 074	512	0	15 429
Upper Volta (Burkina Faso)	0	0	0	0	0	0	0	0	0	0	1 607	312	10	1 929
Zaire	2 000	3 500	3 285	6 259	10 945	2 000	2 985	2 000	1 000	2 024	1 726	2 024	1 055	40 803
Zambia	610	1 800	1 208	1 398	2 061	1 820	1 700	1 842	1 078	2 000	1 284	1 408	180	18 389
Americas														
Brazil	0	0	0	1 255	0	0	0	0	0	0	0	0	0	1 255
Honduras	200	0	0	0	0	0	0	0	0	0	0	0	0	200

Asia														
Abu Dhabi[b]	0	0	0	0	35	15	0	0	0	0	0	0	0	50
Afghanistan	698	0	0	0	0	515	0	0	0	192	224	0	0	1 629
Bahrain	0	0	0	0	70	55	0	0	0	0	0	0	0	125
Bangladesh	0	0	300	0	0	948	4 783	11 331	19 026	0	0	0	0	36 388
Burma	1 500	1 500	76	0	0	0	0	0	0	0	0	0	0	3 076
Democratic Kampuchea	0	1 200	0	0	0	0	0	0	0	0	0	0	0	1 200
Democratic Yemen	0	150	35	0	350	0	220	602	0	300	0	96	62	1 815
Dubai[b]	100	0	0	0	35	105	0	0	0	0	0	0	0	240
India	1 000	0	0	0	0	0	0	1 606	0	0	0	0	0	2 606
Indonesia	1 000	2 350	450	300	0	0	0	0	0	0	0	0	0	4 100
Iran	0	0	0	0	2 026	11 096	0	0	0	0	0	0	0	13 122
Iraq	0	0	0	0	0	5 080	0	0	0	0	0	0	494	5 574
Kuwait	140	0	0	0	0	0	0	0	0	0	0	0	0	140
Lao People's Democratic Republic	100	900	0	500	1 025	0	0	10	0	0	0	0	0	2 535
Lebanon	1 000	1 000	0	283	2 006	1 388	250	502	0	10	65	60	0	6 564
Maldives	0	0	0	70	0	0	0	0	0	0	0	0	0	70
Mongolia	0	0	0	0	210	0	125	125	96	128	0	256	120	1 060
Nepal	450	2 900	2 915	700	1 995	5 875	3 340	2 800	0	1 024	2 048	1 024	0	25 071
Oman	0	0	0	0	454	0	65	0	0	0	0	0	95	614
Pakistan	0	420	4 298	9 005	11 930	3 495	9 085	14 245	7 524	5 000	2 016	1 500	1 000	69 518
Saudi Arabia	0	0	0	287	414	0	0	0	0	0	0	0	0	701
Sri Lanka	0	0	0	0	0	955	65	467	0	0	0	0	0	1 487
Syrian Arab Republic	0	0	0	0	0	1 010	0	0	0	0	0	0	0	1 010
UNRWA	0	0	87	210	0	173	0	171	73	82	163	100	109	1 168
Viet Nam	0	0	67	0	0	0	0	0	0	0	0	0	0	67
Yemen	250	0	315	245	735	210	245	145	450	0	252	100	64	3 011
Europe														
Cyprus	5	0	0	0	0	0	0	9	27	0	0	0	0	41
Yugoslavia	0	0	0	0	0	500	0	0	0	0	0	0	0	500
WHO HQ Miscellaneous	15	50	0	0	0	48	66	0	0	0	0	0	8	187
Oceania														
New Hebrides (Vanuatu)	0	0	0	0	0	0	0	0	0	3	0	0	0	3
Total	14 807	21 316	20 686	32 234	44 741	44 593	34 676	44 802	36 310	21 022	23 657	16 308	4 940	360 892

[a] From 1968 onwards, bifurcated needles started to be used for vaccination, enabling 1 dose to be used for the vaccination of 4 people. Hence numbers of doses are not necessarily the same as numbers of vaccinations performed. In addition, wastage of vaccine in the field must be taken into account. It can safely be assumed that the number of doses should be multiplied by 2 to give the number of vaccinations. Supply of vaccine by WHO was discontinued after 1980 when the eradication of smallpox was confirmed by the World Health Assembly.

[b] Now part of the United Arab Emirates.

therefore decided to request that all vaccine, after testing, should be shipped to Geneva for storage in refrigerated facilities leased by WHO. With this vaccine reserve, WHO administrative staff were able to send out vaccine within 48–72 hours of receiving a request.

During 1967–1979, more than 360 million doses of vaccine were distributed to some 70 countries or organizations (Table 10.9), both vaccine and bifurcated needles being made available to all developing countries that requested them whether or not they were conducting a special eradication programme. Between 1967 and 1969, 15–20 million doses were distributed annually, a figure which increased to 30–45 million doses during the period 1970–1975. Until 1973, however, the balance between demand and available contributions remained a precarious one (Fig. 10.3). Nevertheless, no programme was suspended for lack of vaccine although, in some countries and during some periods, vaccine reserves provided enough for only 1–2 weeks of continuing operations.

Success in ensuring an adequate supply of vaccine must be attributed, in part, to the use of the bifurcated needle from 1968 onwards. Most of the vaccine was supplied in containers which provided 0.20–0.25 ml, sufficient to vaccinate 20–25 persons by conventional scarification methods and 4–5 times that number with the bifurcated needle. For purposes of record-keeping, however, each vial continued to be regarded as containing 20–25 doses. For technical reasons vaccine could not be packaged in vials containing smaller quantities than 0.20–0.25 ml; had it been possible to do so, wastage would have been reduced, since the prescribed practice was to discard any reconstituted vaccine that remained at the end of the day.

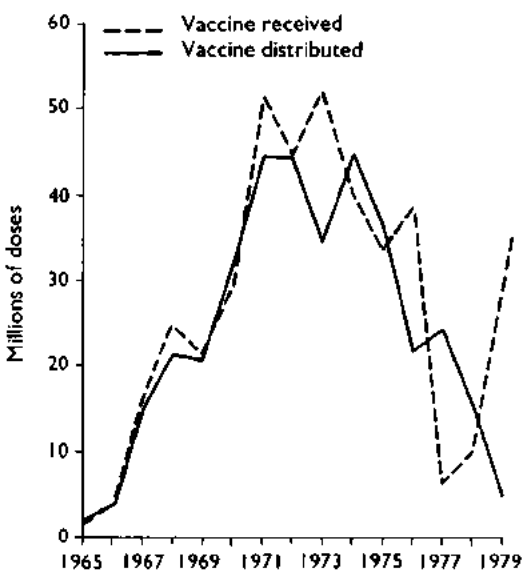


Fig. 10.3. Donations of smallpox vaccine to WHO: numbers of doses received and distributed, by year, 1965–1979.

The vaccine supply depot in Geneva proved invaluable and most vaccine was dispatched from it. In the interests of economy, however, some donated vaccine was sent direct from the producer to recipient countries. When Kenya began to produce more vaccine than it required, stocks were shipped direct from its laboratory to neighbouring countries; Iran's contributions were shipped to Pakistan; South American countries sent vaccine to one another; and Indian bilateral contributions were shipped direct to Bangladesh; Nepal and Sri Lanka in 1975–1976. Several regional offices proposed that regional depots should be established, but the small reserves available made this impracticable. When, in 1976, vaccine reserves at last began to accumulate, a second depot was created in New Delhi at the Regional Office for South-East Asia. Unfortunately, mechanical problems with the refrigeration units and frequent interruptions in the electricity supply made it necessary to close this depot down, and the international reserve of vaccine was subsequently stored by WHO in two locations in Switzerland—Geneva and Lausanne.

Development of Vaccination Devices

New vaccination devices used less vaccine than, and eventually replaced, the traditional scarification instruments used before 1967. Smallpox vaccination with jet injectors, first tested in a pilot project in 1965, was rapid and required only one-third as much vaccine as conventional methods. Jet injectors were widely used in three of the initial major campaigns—in Brazil (see Chapter 12), in western and central Africa (see Chapter 17) and in Zaire (see Chapter 18). However, they were little used elsewhere, partly because of the difficulty of maintaining and repairing them but mainly because the simple, effective and cheap bifurcated needle became available

in 1968, only a year after the Intensified Programme began.

The historical development of the bifurcated needle is described in Chapter 11, in which the needle itself and the containers used for sterilizing needles before use are illustrated (see Plate 11.15). Introduced in 1968 for use with a multiple-puncture technique devised by Henderson and Arita, bifurcated needles had replaced traditional methods in most countries by the end of 1968 and were in use everywhere by 1970. They cost only US$5 per 1000 and could be reused repeatedly after sterilization. Besides conserving vaccine, they were so simple to use that a local villager could be trained in only 10–15 minutes to reconstitute vaccine and to perform effective vaccinations.

Vaccine Practices and Complications

The WHO Handbook recommended that, in endemic and neighbouring countries, everyone, including infants, should be vaccinated. The only recognized contraindication to vaccination related to "individuals who were obviously severely acutely ill" and whose death, if it occurred, might be mistakenly attributed to vaccination. This recommendation was based on the rationale that in endemic areas the risks of complications following vaccination were far lower than those associated with contracting variola major or even variola minor. Moreover, it was recognized that most vaccinations would be performed by vaccinators who would be unable to identify conditions commonly accepted as contraindications to vaccination in non-endemic countries, such as immunological disorders, neoplastic disorders affecting the reticuloendothelial system, and treatment with corticosteroids, antimetabolic drugs or other chemotherapy.

The WHO Handbook described several possible vaccination techniques: multiple-pressure or scratch using a needle or rotary lancet, and the jet injector. An important change from conventional vaccination practice at the time was the recommendation that "the best skin preparation is none at all", and that "if the site is obviously caked with dirt, a cloth moistened with water may be used to wipe the site". This recommendation was based on a number of studies which had demonstrated that conventional methods for cleansing the skin with acetone or alcohol had little effect in reducing the number of bacteria but could destroy or partially destroy vaccinia virus if the vaccine was applied before the liquid had dried.

During the programme, few serious complications were observed which could be attributed to vaccination. The usual response to vaccination—a pustule, with sometimes a sore arm and fever—was readily tolerated although it caused some people to refuse vaccination—for example, agricultural workers during the harvest period. Disseminated vaccinia was observed in only a few patients. Cases of post-vaccinial encephalitis, a far more serious complication, undoubtedly occurred but because of the large number of prevalent illnesses which caused cerebral symptoms (e.g., malaria), it was difficult to know whether cases of encephalitis-like illness were complications of vaccination or were due to other causes. An unusual group of complications occurred in Ethiopia among nomads of the northern Ogaden desert, a number of whom, following primary vaccination, developed a deep, non-pustular crateriform lesion at the vaccination site which penetrated as deep as the muscle fascia. All those affected reported that they had applied the ashes of a thorny shrub to the lesion. Efforts to interest pharmacologists in this phenomenon were unsuccessful but the problem ceased when a sulfa powder was distributed and the nomads were advised to use this instead of the ashes.

SURVEILLANCE AND NOTIFICATION OF SMALLPOX CASES

Whereas, up to 1967, smallpox eradication programmes consisted entirely of mass vaccination campaigns, from 1967 onwards they also included surveillance. Little attention had been given to surveillance and the notification of smallpox cases either internationally or within countries up to that time; in the endemic countries, there were no nationally organized programmes designed to investigate and contain reported outbreaks. From 1967, however, the indicator used for measuring the progress of the programme ceased to be the total number of vaccinations and was replaced by the numbers of reported cases of smallpox and of endemic countries. Epidemiological analysis of the cases provided important information from the point

of view of the strategy and tactics to be employed and the allocation of resources.

The difficulty of explaining the concept of surveillance to programme staff and of gaining their acceptance of it was not appreciated, however, when the programme began. Mass vaccination campaigns were familiar and well understood but because they were complex to organize and execute, little time and few resources were usually available for surveillance. Incorporating into programmes what had seemed to be a simple, basic concept required much of the time and energy of the senior WHO smallpox eradication programme staff.

The Concept of Surveillance

The concept of a nationally supervised programme for reporting and investigating smallpox cases and containing outbreaks had, as its antecedent, the disease surveillance programmes of CDC in the USA (Langmuir, 1963). Dr Alexander Langmuir, its chief epidemiologist, had fostered the concept of surveillance since his appointment in 1949. He attributed the genesis of the concept to William Farr, who had been the superintendent of the Statistical Department of the Registrar General's Office of England and Wales in the 19th century. Farr's epidemiological analysis of cases and deaths over many years and by age group, area and season, made it possible to formulate hypotheses as to the way in which diseases were spread, which in turn suggested possible control measures and enabled forecasts of future trends in disease incidence to be made.

Dr Langmuir defined surveillance as the "continued watchfulness over the distribution and trends of incidence through systematic collection, consolidation and evaluation of morbidity and mortality reports and other relevant data". He pointed out that "intrinsic in the concept is the regular dissemination of the basic data and interpretations to all who have contributed and to all others who need to know". In developing surveillance in the USA, he focused primarily on diseases for which control measures were available, beginning with malaria, sylvatic plague and leprosy, and subsequently extended it to include diphtheria, poliomyelitis and other diseases. Working with state and local health officials, he and his staff obtained detailed information about reported cases, including confirmation of the diagnosis by laboratory study and basic data regarding age, sex, race and place of residence and, depending on the disease, information regarding vaccination status, possible place of exposure, etc. These data were regularly analysed, appropriate control measures recommended and surveillance reports prepared and widely distributed.

Henderson had worked with Dr Langmuir since 1955 and had served from 1961 to 1965 as chief of the Surveillance Section at CDC. It seemed to him only logical to endeavour to apply the principles of surveillance to the eradication of smallpox. This was stated in the Director-General's report to the Nineteenth World Health Assembly (World Health Organization, 1966b; see Chapter 9), which Henderson, as a consultant to WHO, had helped to prepare. This approach was strongly supported by Dr Raška, Director of the Division of Communicable Diseases, who had been a keen proponent of epidemiological surveillance while working in his own country, Czechoslovakia (Raška, 1964).

The concept of surveillance as applied to the smallpox programme was succinctly described in the WHO Handbook as follows:

> "The primary objective of the smallpox programme is the eradication of this disease. Surveillance is thus an essential component of the programme since the term 'eradication' implies that the number of indigenous cases of smallpox reach '0' ... Surveillance represents a great deal more than case reporting alone. It is composed of several components:
>
> (a) The routine, systematic collection of data, amplified appropriately by special field investigations and studies
> (b) The concurrent analysis and interpretation of reported data and studies
> (c) The initiation of appropriate definitive action including field investigation, epidemic control, modification of operational campaign procedures, recommendations regarding vaccination, etc.
> (d) Widespread dissemination of the compiled and interpreted data to principal reporting sources and to others concerned with disease control activities."

The Routine Systematic Collection of Data

A reporting network which provided for the collection of epidemiological data regarding each case of smallpox was the foundation of the system. Its goal was to ensure that each week all known cases of smallpox would be

reported by the peripheral health units in each country, through intermediate administrative units, such as districts and provinces, to national and, ultimately, to international authorities. The concept was simple, but there were formidable problems at every level in perfecting such a system.

Although this section deals primarily with surveillance at the international level, certain features and problems of national data collection systems need to be described in order to appreciate the quality of the data being provided in 1967 to WHO by national authorities in the endemic countries.

Reported cases of smallpox, which would be routinely notified if the system were functioning properly, inevitably represented only a portion of all the cases which actually occurred. The basic network of reporting units—health clinics, hospitals and dispensaries—documented only those who presented themselves for treatment. Many patients had no access to health care or did not go to health care units for fear of unwanted forcible isolation in a hospital or because they knew that there was no effective treatment. They could be discovered through searches or by field investigations of known outbreaks, but few health services undertook such activities. Even where there was complete notification of all cases seen by health units, the data provided only an indication of trends in incidence and of the geographical dispersion of the disease.

In all endemic countries, the notification networks themselves were seriously deficient. Usually, health units were supposed to provide weekly or monthly summaries of the number of patients seen, but smallpox was often only one of 25–50 different diseases that they were expected to report. Poorly supervised, overworked health staff customarily devoted little time to the preparation of lengthy reports which rarely led to any action being taken. Some regularly submitted reports to higher authorities but many did so only occasionally. In intermediate administrative units—such as states or provinces—and at national level, data were usually received and tabulated, often after extended delays, by clerical personnel whose responsibility was limited to ensuring that the data were entered accurately. Little notice was taken of whether all units reported or when they did so, and because the data were rarely used in programme operations, there was little incentive to improve the system.

All countries were expected to send to WHO weekly reports of cases of the so-called quarantinable diseases (smallpox, cholera, plague, yellow fever and typhus), and to indicate the areas in which they had occurred. Such routine reporting had been the practice since the adoption of the International Sanitary Convention of 1926, when receipt and publication of the information was the responsibility of the Health Organisation of the League of Nations, a function assumed by WHO on its foundation.

In WHO, in 1967, the receipt and tabulation of data on the quarantinable diseases was the responsibility of the International Quarantine unit, which later became the Epidemiological Surveillance and Quarantine Unit and in 1971 was renamed the unit for the Epidemiological Surveillance of Communicable Diseases; for convenience, it is referred to below simply as the "WHO quarantine unit". Reports were received direct from the countries concerned rather than through the WHO regional offices, and indicated the number of reported cases in each administrative unit, or "local area" as it was called, such as a district or county. The reports also specified which of the local areas were newly infected and which could be declared free of the disease. Each week a lengthy list of the existing and newly infected local areas in each country was published in the *Weekly epidemiological record* for each of the quarantinable diseases. In theory, this enabled quarantine officers and others concerned to determine whether or not a traveller had been in an area in which one of the diseases was present and to take appropriate measures. In practice, most health authorities recognized that reporting everywhere was deficient and usually considered the whole of a country to be infected if infection was present in any of its local areas.

The WHO quarantine unit also tabulated the number of cases reported. The data so compiled were considered to be the provisional official totals of cases, pending later receipt of annual reports from national governments. Such annual reports, when compiled and published some 3–4 years later by the WHO Division of Health Statistics, constituted the final authoritative international record of disease incidence. No attempt was made to reconcile the data in the provisional reports with those in the annual reports, and national authorities were seldom questioned as to the accuracy of the information provided.

Changes in the International Data Collection System

The inadequacy of the routine data collection system for smallpox cases had been recognized in 1967 but not until much later did it become apparent just how inadequate it was. Smallpox eradication programme staff had assumed that, because smallpox was one of the principal diseases subject to international quarantine agreements and because most infected countries submitted weekly reports, albeit after long delays, it was one of the better-reported diseases. However, field investigations soon showed that not more than 1 case in 20 was being notified. Later, through facial pockmark surveys, it became apparent that probably not more than 1 case in 100 was being reported and, in some countries, such as Ethiopia, perhaps 1 in 1000. Despite the incompleteness of reporting, however, the notified data proved to be important from the beginning of the programme for decisions about priorities and resource allocations and for assessing progress; ultimately, they were essential in determining that transmission had been interrupted and in certifying that eradication had been achieved.

Efforts to improve the system began with the initiation of the Intensified Programme. Deficiencies became apparent almost immediately when WHO staff attached to national smallpox eradication programmes cited national data which differed from those reported to the WHO quarantine unit. When efforts were made to reconcile the two sets of figures, it was discovered that, in many ministries of health, there were two sets of data, one compiled by a statistical unit and one by smallpox eradication programme staff. The statistical unit's data were taken from routine reports submitted by states and provinces, while those of the smallpox eradication programme office were often revised to take into account additional cases discovered during field investigations, reports obtained by the staff from states or provinces which had failed to file reports with the statistical office, and information on reported cases which had been mistakenly diagnosed. It was usually of no importance to national eradication programme staff whether the statistical unit's data differed from theirs or not, since such differences had no bearing on their operations.

Through correspondence with the countries and discussions with the WHO quarantine unit, WHO smallpox eradication staff sought to obtain the most complete national data available. In some instances, it was possible to obtain revised national figures extending over many months or several years, which usually showed much larger numbers of cases than those reported by the national statistical unit. The WHO quarantine unit did not take cognizance of such information because its responsibility was to compile only the current data officially reported to WHO and to maintain the registry of local infected areas. For the first three years of the Intensified Programme, two sets of data were maintained at WHO on smallpox incidence during the current and immediately preceding years. Depending on the WHO publication, sometimes one and sometimes the other set of data was used, but smallpox surveillance reports always used Smallpox Eradication unit data. In 1969, it was agreed that the Smallpox Eradication unit would assume the responsibility for all current data on smallpox cases and infected local areas, a procedure which reduced confusion and conserved manpower.

Meanwhile, through personal contact, correspondence and the publication of summaries of the smallpox situation in the *Weekly epidemiological record*, governments were urged to report more promptly and gradually began to do so. However, even as late as May 1970, reports from 5 countries were more than 4 weeks overdue and not until 1972 were reports received promptly from all the states of India (see Chapter 15). By the end of 1972, however, few reports from countries were delayed by as much as 2 weeks.

In 1970, another question arose in WHO Headquarters regarding what should constitute the authoritative international record of smallpox incidence. In that year, staff in the Division of Health Statistics observed that the numbers of smallpox cases in governments' annual summaries of disease incidence (a third data set) did not always agree with the data compiled by the Smallpox Eradication unit. Upon investigation, it was found that the differences usually reflected the fact that two sets of data had been compiled nationally. In other instances, clerical errors had been made in the annual summaries submitted, sometimes resulting, for example, in smallpox cases being reported by countries remote from endemic areas and with no known importations. These errors were quickly corrected by the governments concerned when they were

Table 10.10. World total of smallpox cases as recorded in April 1967[a] and as revised in 1987

Date recorded or revised	1959	1960	1961	1962	1963	1964	1965	1966
April 1967[a]	81 444	60 956	85 594	82 413	99 599	49 956	64 321	65 512
1987 revision	96 571	67 127	90 588	98 759	133 791	77 295	112 228	92 650
Percentage increase	19	10	6	20	34	55	74	41

[a] Unpublished World Health Assembly document A20/P&B/7.

brought to their attention but such data had been accepted without question in previous years. Towards the end of 1970, it was decided that the data compiled by the Smallpox Eradication unit, based on what it considered to be the most accurate national data, should be used in WHO publications. Thus, what had once been three different sets of smallpox data in WHO became one.

The possible suppression of reports of smallpox cases by national authorities was a continuing concern, although it did not happen often. Such suppression was most marked in western Asian countries and resulted, in part, from the adverse consequences of reporting cholera cases during a recent pandemic. These reports had induced other governments to impose unwarranted barriers to trade and travel which had caused serious economic losses. Some feared that reports of smallpox might result in similar measures being taken and therefore suppressed them. Cases of smallpox, especially when they were numerous, were not easy to conceal, however, and WHO learnt about them from many sources, including embassies, travellers and persons working in international organizations. All rumours of outbreaks were followed up by WHO by telex and by correspondence and sometimes by personal visits. Even when it was certain that smallpox was present, publication of the information without official government approval was diplomatically impossible. The suppression of reports had 2 adverse consequences: it jeopardized the credibility of the programme and the eventual acceptance of global eradication; and it made it difficult for the countries concerned to mobilize health resources and community support in order to control the outbreaks. Although most health authorities eventually cooperated in reporting, 4 did not acknowledge the existence of cases until many months or years later, and 3 eventually experienced major epidemics. These are discussed in Chapter 22 (Somalia) and Chapter 23 (Iran, Iraq and the Syrian Arab Republic).

Throughout the programme, national totals of smallpox cases were corrected whenever better information became available so as to reflect more accurately the actual incidence. Data for 1967–1977 were most carefully scrutinized, but changes were also made in data for a number of years preceding 1967. For example, the data presented in this book show global totals for smallpox cases between 1959 and 1966 substantially greater than those in the report (prepared in April 1967) submitted by the Director-General to the Twentieth World Health Assembly. The totals for the years 1959–1962 are 6–20% greater and those for 1963–1966 are 34–74% greater (Table 10.10). The larger discrepancies after 1963 reflect the fact that smallpox eradication staff in most countries reviewed and revised national and state or provincial data only from 1963 or 1964 onwards.

International Surveillance Reports

A basic precept of surveillance is, as has already been quoted from the WHO Handbook, the "widespread dissemination of the compiled and interpreted data to principal reporting sources and to others concerned with disease control activities". Accordingly, the first of what were intended to be quarterly international surveillance reports was issued by the Smallpox Eradication unit as a mimeographed document in September 1967. It was sent to some 200 persons, principally WHO staff concerned with smallpox eradication and national programme directors. A second report was issued in December 1967 and a third prepared in March 1968. Distribution of the third report was stopped, however, by senior WHO management staff, who believed that there were too many WHO reports and therefore decided to suspend most of them pending a

full review of WHO's publication policies. Eventually, it was decided that smallpox surveillance reports should be discontinued.

The coordination of a global programme was difficult enough, but without some mechanism for disseminating information on its status and the progress being made, the task appeared impossible. The matter was discussed in WHO in a series of difficult meetings extending over 8 weeks, and it was finally decided that a brief report on smallpox could be inserted periodically into the *Weekly epidemiological record*. From May 1968 onwards, such reports were published every 2–3 weeks.

Use of the *Weekly epidemiological record* had both advantages and disadvantages. The main advantage was that it was a well-established periodical with a circulation of some 5000 copies which reached a far larger audience than was possible with the mimeographed report. The disadvantage was that it published only epidemiological data, to the exclusion of other information which the smallpox eradication programme needed to have disseminated, such as the results of tests on the bifurcated needle and techniques for its use, and reports of the deliberations of relevant expert committees and scientific groups. Moreover, the periodical was normally sent by surface mail and not all WHO and national smallpox eradication programme staff had access to it. To solve these problems, it was agreed that additional copies of the smallpox surveillance section of the *Weekly epidemiological record* would be printed and sent by air mail, together with other special reports dealing with smallpox, to the 150–200 persons concerned with the programme. Thus began the practice of a special mailing every 2–3 weeks to all WHO and senior national smallpox eradication programme staff, a practice which ensured more rapid delivery than the traditional channels of communication through the regional offices. The WHO/SE, SE and SME series of documents listed with the references at the end of this book constituted most of the papers so distributed. Accounts by field staff were seldom prepared without considerable persuasion because, for many, English was not their mother tongue and few were experienced in writing papers for publication. A promise that smallpox eradication programme staff would edit all suitable papers increased the number submitted. Although the editorial burden was staggering, the papers proved invaluable in documenting useful observations made in the course of the programme and in fostering evolutionary change.

Following the incorporation of the smallpox surveillance reports into the *Weekly epidemiological record*, its editor, Dr Ian Carter, began to transform the publication itself. Once unkindly referred to as "the laundry list of infected local areas", the periodical gradually became a substantive document dealing with many diseases and reaching an increasingly wider public. With time, the smallpox surveillance reports gradually increased in length and frequently appeared on the first page, but the prominence given to smallpox eradication troubled the responsible Assistant Director-General, who felt that other important disease problems were not receiving sufficient attention. He therefore directed that the smallpox reports should be relegated more often to the inside pages. Thereafter, by tacit agreement, the smallpox surveillance report appeared on the front page of the *Weekly epidemiological record* only twice a year, when the semi-annual summaries were published.

RESEARCH

In 1967, few administrators or scientists believed that additional research was needed or would contribute to the achievement of smallpox eradication. This was understandable. A smallpox vaccine had been available and in use for more than 150 years and the commercial production of a thermostable vaccine had been perfected. The epidemiology of the disease under many different circumstances and in many countries had been described and the feasibility of eradication had been demonstrated in a number of developing countries. The basic task, as most saw it, was administrative—primarily that of organizing programmes to deliver vaccine to the population of the endemic countries. The attitude towards research was similar to that which had prevailed when global malaria eradication began in 1955. In that programme, research had been largely abandoned until 10 years later, when, with the programme progressing poorly, it was recognized that additional tools and different strategies were required. By then, however, competent and experienced research staff had turned to other fields. It was an important

lesson, and one which those in the Smallpox Eradication unit believed should be heeded.

In 1967, little smallpox research was in progress, and only US$20 000 were allocated in the WHO budget for the support of such research. With so few resources and with only 4 medical officers in the Smallpox Eradication unit in Geneva, WHO could not undertake a comprehensive, well-organized research programme. However, it was hoped that field staff might be able to make significant contributions and, to stimulate their interest, some 20 areas requiring research were identified in the WHO Handbook. In consequence, many field staff undertook and participated in a wide range of important studies from the beginning of the programme.

One research area was of paramount importance—to establish with certainty whether there was any natural reservoir of variola virus. Since yellow fever eradication had been thwarted by the unexpected discovery of an animal reservoir, and in the light of the suggestions then being made that there might be a simian reservoir of malaria, the question naturally arose whether there might also be an unrecognized natural reservoir of smallpox. This question was dealt with in a series of planned studies involving many different investigators and laboratories.

Substantial amounts were eventually spent in support of research by many laboratories and, although no quantitative data are available, they were far greater than the sums provided by WHO. Of especial note are the contributions of CDC in Atlanta, the Moscow Research Institute for Viral Preparations, the National Institute of Health in Japan, the Department of Virology of St Mary's Hospital Medical School in London, the National Institute of Public Health in the Netherlands, Wyeth Laboratories in the USA, the Calcutta Institute of Tropical Medicine in India, the Public Health Institute in Bangladesh, the Pakistan Medical Research Centre in Lahore and the University of Maryland School of Medicine in Baltimore, whose scientists worked in Pakistan.

In retrospect, it is unlikely that the global eradication of smallpox would have been achieved without the broader understanding of smallpox, its virology and epidemiology, which the research conducted after 1967 provided. The results of such research include: the redefinition of the epidemiology of smallpox and because of this, a change in the strategy so as to place increased emphasis on surveillance and containment; an improved understanding of the efficacy and duration of vaccinial immunity and, as a result, changes in practices pertaining to revaccination; a great improvement in vaccine production and testing procedures; the development of a new technique of vaccination, employing a new instrument; the genetic mapping of variola and vaccinia viruses to provide new insights into the relationships of the orthopoxviruses; the discovery and characterization of human monkeypox; and the development of sample survey techniques.

The research programmes and the observations made are described in detail in the appropriate chapters of this book. For this reason, only the highlights of some of them are described here so as to place them in the context of the development of the global programme.

A Natural Reservoir of Smallpox

From 1967 onwards, attention was focused on determining whether smallpox virus could persist in nature outside the human being. If smallpox were found to persist in an enzootic state, or if there were a closely related animal orthopoxvirus which could infect humans and whose transmission could be sustained in man, it was unlikely that smallpox could be eradicated. No less important was the question of how long variola virus could persist in nature, since this, too, had implications for the possible recurrence and re-establishment of infection in areas in which transmission had been interrupted. These problems are discussed in Chapters 2, 29 and 30.

The first review of the available data dealing with a possible animal reservoir of variola virus was published by Arita & Henderson (1968). They reasoned that, if there were a natural reservoir of variola virus, non-human primates were important candidates. As is discussed in the paper, a few reports had suggested that smallpox outbreaks did occur naturally in primates, but most of them dated from the 19th century. In view of the extent of endemic smallpox in countries in which primates were found and the paucity of reports of possible outbreaks in the present century, it seemed unlikely that primates really were a reservoir, but confirmation was

required. Also of interest was the closely related monkeypox virus, first described by Magnus et al. (1959) after an outbreak among a colony of laboratory primates and subsequently reported in 3 other laboratories. No human infection had occurred, but because adults in close contact with the animals were few and probably well vaccinated, no conclusions could be drawn about the possible infectivity of the virus for man. To study the matter further, Arita, in 1967, conducted a survey of 26 biological institutions which handled large numbers of primates to ascertain whether other, unpublished, outbreaks had occurred, to discover the circumstances associated with such outbreaks and to find out whether there had also been human infections. Five other outbreaks among primates came to light but no human cases. Almost all the illnesses occurred in Asian species and were clinically similar to those observed when primates were experimentally infected with smallpox.

To consider the problem of monkeypox and to develop a research agenda, a meeting of investigators from 6 laboratories (the Informal Group on Monkeypox and Related Viruses) was convened by WHO in March 1969 in Moscow. Thereafter, the investigators met every 2 years to plan a wide range of studies on the experimental infections of primates and other mammals with variola and monkeypox viruses and serological surveys of primates in Africa and Malaysia. New impetus to the efforts was given by the discovery of the first human monkeypox cases in 1970, and the working group was expanded to include epidemiologists and mammalogists. Subsequently, special field surveys were initiated to define the problem; these continued up to 1986 (see Chapter 29). They provided important substantiating evidence that no mammalian reservoir of smallpox existed and that monkeypox, confined to villagers in the tropical rain forest, could not be maintained by person-to-person transmission.

A second problem was to determine whether variola virus could persist in nature on fomites such as cloth or as scabs, and cause infection in man many months or even years later. That this was a cause for concern had been suggested in studies by investigators in the Netherlands, who demonstrated the survival of variola virus in scabs for as long as 13 years (Wolff & Croon, 1968). Whether the virus was of sufficiently high titre or in a form such that man could be infected was unknown. The possible persistence of variola virus in nature was also suggested by anecdotal accounts, dating from previous centuries, of cases and outbreaks following the exhumation of the body of a person who had died of smallpox and of cases said to have occurred in newly reoccupied houses in which a smallpox patient had died months or years before. The validity of these observations was uncertain because all had been reported from areas in which smallpox was then widely endemic. Also of concern were variolators in Africa and Asia, who were known to collect and retain scabs and pustular material for periods of a year or more.

To determine the possible risk of the persistence of viable variola virus under field conditions required many different epidemiological and laboratory studies. Laboratories in Bangladesh and India undertook to determine the duration of the viability of variola virus under different conditions of temperature and humidity. Epidemiologists were instructed to document with care the source of infection of cases, especially those in which there was a possibility of exposure to virus which had persisted in the environment. Special efforts were made to determine the source of infection of outbreaks in all countries thought to be free of smallpox. Variolators were contacted and questioned in detail about their experiences in retaining smallpox material, and variolation material was obtained from them for titration in the laboratory. The results of these studies are described in Chapters 2 and 30. Ultimately, it became clear that, even under favourable conditions of low temperature and humidity, the virus did not survive for more than a few days or weeks in a form which could induce infection, unless inoculated, as in variolation. Even in this case, variolators reported that they had difficulty in inducing infection with material retained for longer than a year.

Epidemiological Observations

Of the many epidemiological observations, the most important were those which indicated that surveillance and containment should be accorded a much higher priority than had initially been appreciated. The first and most comprehensive of the field studies were those conducted in Pakistan and Bangladesh (then East Pakistan) during 1965–1968

and directed by scientists from the University of Maryland, USA, and the Pakistan Medical Research Council (see Chapters 4 and 14). In careful studies of the characteristics of the spread of smallpox, they showed that, even in highly infected areas, cases tended to occur in clusters rather than being widely disseminated, and that the disease spread less rapidly and less easily than was commonly believed and only through close personal contact. Moreover, during periods of seasonally low transmission, they found few continuing chains of smallpox transmission, mainly in urban areas. These characteristics suggested that the spread of smallpox could be more rapidly interrupted if greater emphasis were placed on the discovery of cases and the containment of outbreaks, especially during the season when transmission was at a low level and in urban areas. Observations in eastern Nigeria in 1967, in India in 1968, and in Brazil and Indonesia in 1969 confirmed the practicability of this approach. These observations were made known to all smallpox eradication programme field staff, but the basic concepts of surveillance and containment were slow to be accepted, having to be rediscovered and/or demonstrated in special programmes in most areas before they were incorporated into programmes.

Many other studies and observations arising from field programmes led to changes in strategy and operations (see Chapters 4 and 12–22). Among these were studies which showed that variola minor could persist for long periods among small nomadic groups, necessitating special surveillance procedures; that women in Afghanistan, confined to their houses by the practice of purdah, were mostly immune owing to a previous attack of the disease or to vaccination and that special vaccination programmes for them were unnecessary; and that the airborne transmission of variola virus over a distance was possible but only under exceptional circumstances and within buildings and so was not of concern. Methods were developed by which to estimate the incidence of smallpox in previous years, and special studies documented the frequency of persistence of facial pockmarks, observations which were important in deciding on the strategy for certification.

Few investigations were undertaken which required substantial laboratory support, partly because many of the studies required no more than physical observations of lesions or scars, and partly because few laboratories were equipped to process large numbers of specimens. Studies which did involve laboratory support were conducted in Bangladesh, India, Somalia and Zaire and concerned the behaviour of other animal poxviruses (see Chapter 29) and the pharyngeal excretion of variola virus among contacts of patients (see Chapter 4).

Vaccination Practices

Through research, not only did better vaccination instruments come into universal use but other vaccination practices also changed. Policies with regard to the youngest age for vaccination and the recommended frequency of revaccinations were changed. In most endemic countries, in 1967, primary vaccination was not given until the child had reached 3–12 months of age, and revaccination was performed every 3–5 years. The vaccination of neonates, however, had long been known to be a safe and effective practice and, in fact, had become a standard procedure in some countries of eastern Asia (Urner, 1927; Moodie & Cheng, 1962). Dr A. R. Rao's confirmation of these observations, in a WHO-supported programme in southern India, served to encourage wider acceptance of the practice, which made it easier to achieve higher levels of vaccination coverage during mass vaccination campaigns and enabled very young children to be protected during outbreak containment. That immunity following vaccination might be far more long-lasting than had been thought was suggested by field observations which showed that, even in well-vaccinated populations, 80–95% of cases occurred among those who had never been vaccinated. More precise measurements of vaccine efficacy subsequently confirmed that high levels of immunity continued for at least 10–20 years. These findings, documented early in the programme, led to a shift in the emphasis of vaccination campaigns from an effort to reach the entire population to approaches which would ensure that everyone had received primary vaccination at some time.

Vaccine Production and Testing

In 1967, much was known about commercial methods for the production of freeze-dried smallpox vaccine and a production manual

was issued by WHO in 1968 (SE/68.3 Rev.2). Nevertheless, several studies were undertaken to examine certain aspects of the process, such as the optimum day for harvest to ensure maximum virus yield, the yields of virus produced by different strains, and alternative methods of purifying the vaccine and reducing bacterial content (see Chapter 11). Testing procedures were thought to have been standardized, but when different laboratories obtained quite different results on testing the same batches of vaccine, studies showed that slight but previously acceptable variations in technique were responsible; these were corrected. Although collaboration among potentially competing production laboratories is uncommon, this was not the case in the smallpox eradication programme. Laboratories in Canada, Czechoslovakia, the Netherlands, the USSR and the USA cooperated and shared information in solving problems, and their findings were communicated to all production laboratories.

Characterization of the Orthopoxviruses

An examination of the similarities and differences between variola virus and other orthopoxviruses was important in assessing the likelihood that such a virus might, in some manner, mutate to a form whose virulence and transmissibility were such that infection could be sustained in man. Support for studies aimed at a more precise characterization of orthopoxviruses was provided by WHO to laboratories in London and Birmingham (England), Atlanta (USA), Tokyo (Japan) and Moscow (USSR), each of which committed substantial additional resources of its own. The importance of these studies increased with the discovery, in the early 1970s, in the Netherlands and in the USSR, of virus strains apparently isolated from animals and having characteristics indistinguishable from those of variola virus. Until the discovery of restriction endonucleases, which enabled the DNA structure of viral strains to be analysed, these analyses relied on biological markers, such as growth properties in different animals and cells and the optimum temperature for growth. The techniques were complex and time-consuming and the interpretation of the results was often uncertain. Ultimately, restriction endonuclease analyses of viral DNA proved of the greatest value. The isolates of variola-like viruses obtained from animals in the Netherlands and the USSR were eventually shown to have been laboratory contaminants (see Chapter 29) and genetic analysis showed that it was highly unlikely that any of the large number of animal orthopoxviruses could be transformed by one or even several mutational steps into a virus which resembled variola virus.

Summary

Even from this brief recapitulation, it is apparent that the epidemiological and laboratory research stimulated and coordinated by WHO contributed materially to the achievement of smallpox eradication. The effort was not, overall, a wholly integrated and comprehensively planned effort and was only modestly supported by WHO funds, but it was remarkably well directed towards finding solutions to operational questions and needs. Of signal importance was the ready cooperation of the investigators and their willingness to make available their papers and their data before publication. This, in turn, permitted the earliest possible application of new findings.

STRATEGIES AND TACTICS IN THE EXECUTION OF NATIONAL PROGRAMMES

Introduction

A survey of the approaches adopted in national vaccination campaigns and in surveillance and containment measures is provided in this section as an introduction to Chapters 12–22, which describe field operations in the various countries. The principles and practices were common to most but many aspects of the structure and method of operation of each national programme were unique, since each had to be adapted to the prevailing administrative, social, demographic and geographical conditions and each changed with time in response to experience and needs.

As has previously been described, the basic strategy for national programmes called for 2 different activities: (1) mass vaccination campaigns, assessed for both coverage and take rates by special teams; and (2) surveillance and containment of outbreaks. As infor-

mation accumulated on the extent of vaccinial immunity and the epidemiology of smallpox in the different countries, it became apparent that mass vaccination campaigns, particularly in Asia, were less important than the discovery and containment of outbreaks. Vaccinial immunity was found to be generally higher in most countries than had been expected and, in some countries, smallpox cases were so few that a comparatively simple surveillance and containment programme could serve to interrupt transmission.

Because mass vaccination campaigns were the traditional control method and were most readily accepted by national authorities, all endemic countries and many of those adjacent to them conducted such campaigns. While perhaps unnecessary in some areas, they served an important additional function in that vaccination teams, moving from village to village, were able to detect unreported cases of smallpox or to confirm its absence.

Surveillance–containment programmes, however, were frequently slow to begin, because the logistics of mass vaccination campaigns were so demanding and the techniques unfamiliar. Some programmes, adopting the tactics used for malaria eradication, deliberately delayed the commencement of surveillance until mass vaccination had been completed, an activity which they equated with the "attack phase" of the malaria programme. It was not always easy to persuade national programme staff and WHO smallpox eradication advisers that surveillance–containment operations should begin immediately and be accorded as high a priority as mass vaccination.

The importance of surveillance and containment was emphasized in discussions at the World Health Assembly and by Health Assembly resolutions in 1968 and 1969, and again by an explicit resolution of the Executive Board (EB45.R20), subsequently endorsed by the Twenty-third World Health Assembly (1970), in which the Board requested "all countries to take appropriate steps to improve further case-reporting and to adopt as an objective the immediate investigation and containment of all reported cases and outbreaks of smallpox from 1970 onwards" (World Health Organization, 1973a). Much effort was devoted to accomplishing this objective and demonstration-type programmes were organized to encourage it. Its importance was further reinforced in numerous publications and communications. From 1969 onwards, smallpox eradication staff at WHO Headquarters recommended that surveillance–containment measures should be given priority over mass vaccination but because change was slow to come, they proposed in 1972 that all resources should be directed to surveillance–containment and that mass vaccination should be stopped. Although this proposal did not reduce the interest in mass vaccination on the part of most national authorities, it ultimately served to focus sufficient attention on surveillance and containment to permit the development of satisfactory programmes. To suggest that mass vaccination was unnecessary in any circumstances was recognized to be extreme and simplistic but it seemed necessary to do so at the time in order to alter national strategies. This was not without certain repercussions, however. By the time the emergency programme was introduced in Somalia in 1977, the principle of surveillance–containment had acquired a doctrinal quality and some WHO smallpox eradication advisers argued that it was heretical to conduct mass vaccination campaigns in any area, whatever the need (see Chapter 22).

The most important factors determining the success of all programmes were the quality of senior staff at the national level and their willingness to go into the field to see for themselves what progress was being made, to find solutions to problems and, by their example, to encourage lower-level supervisors to do likewise. In most countries, it was both traditional and accepted for supervisors, even at the lowest administrative levels, to remain in their offices. Many considered it demeaning to leave them, and those who wished to do so frequently lacked the necessary authority or transport. Supervision was customarily provided through verbal orders and written directives, and the results of programmes were assessed, if at all, through written reports, often of dubious veracity. In the smallpox eradication programmes, the supervisors were provided with transport, and WHO staff and consultants, by their example, played an important role in helping to change traditional patterns. Frequently, it was found that national and WHO smallpox eradication programme supervisors were almost the only supervisory staff to visit health programmes in the field or district centres and dispensaries. This type of frequent contact between supervisors and field personnel not only served to

resolve problems more rapidly and to redirect activities more efficiently but also proved invaluable in sustaining morale and interest.

In the following pages, the general practices followed in mass vaccination campaigns are discussed first, followed by those in the surveillance–containment programmes.

Mass Vaccination Campaigns

Objectives

Before 1967, the smallpox eradication strategy relied entirely on mass vaccination in the belief that, when the proportion of susceptible persons in the population had been substantially reduced, transmission would cease. Until 1964, it had been assumed that this would occur when 80% of the population had been successfully vaccinated within a period of 4–5 years (World Health Organization, 1959b), an arbitrary figure with no scientific basis. Between 1959 and 1966, mass vaccination campaigns succeeded in eliminating smallpox in a number of countries, but whether 80% of the population had been successfully vaccinated is unknown as little attempt was made to assess the results of the campaigns and knowledge of the numbers of vaccinations performed is of little value because most of the vaccine used was thermolabile and lacked potency, so that many vaccinations were undoubtedly unsuccessful.

The WHO Expert Committee on Smallpox (1964) declared the figure of 80% to be insufficient and recommended that the goal should be to vaccinate 100% of the population. The only basis for this recommendation was the observation in India that smallpox persisted in some areas despite vaccinations which, in the numbers reported, were equivalent to 80% or more of the population. The Committee, however, ignored the information from field studies in India itself (later critically examined by Gelfand, 1966), which showed that the proportion *successfully* vaccinated fell far short of 80% because of the use of subpotent vaccines and the frequent revaccination of the most easily accessible groups. The proposition that smallpox could be eliminated by successfully vaccinating 80% of the population was thus discarded but on scientific evidence just as inadequate as that on which it had originally been based.

The WHO Handbook also recommended that mass vaccination campaigns should aim at successfully vaccinating 80% of the population. The figure was an arbitrary one, intended only to indicate what could reasonably be expected in a well-conducted programme.

One can only speculate as to how many countries might have succeeded in interrupting transmission simply with an effective mass vaccination campaign reaching 80% or more of the population. However, from the authors' review of programmes conducted after 1967, it would appear that mass vaccination alone resulted, or probably would have resulted, in the elimination of smallpox in South America and most African countries but not in the densely populated countries of Bangladesh, India, Indonesia and Pakistan. Even in America and Africa, however, surveillance programmes were necessary, to provide the basis on which to be able to certify that transmission had been interrupted.

Administration

The mass vaccination campaigns were conducted by national health staff, usually with technical advice and material assistance from WHO and other agencies. A full-time programme director and unit were usually made responsible for the programme; in the larger countries, special units were also created at state or provincial levels. The programme staff were an integral part of the health ministry and worked with existing health service units, coordinating their activities whenever possible with those of other special programmes, such as those for BCG vaccination, malaria eradication and leprosy and yaws control. Their salaries were paid by the respective governments, although in some cases WHO supplemented the salaries of some senior staff to enable them to work full time in the programme. In most countries, international assistance bore the costs of all supplies and equipment as well as living allowances and travel costs for surveillance teams and the costs of petrol and vehicle repairs. After 1973, when many temporary workers began to be employed to intensify programmes in the remaining endemic countries of Asia and eastern Africa, their salaries were also met by funds from international assistance.

Preparations

The necessary preparations for a vaccination campaign could be completed within a matter

of a few weeks or a month or two, but most programmes did not begin until 6–18 months after an agreement had been signed between the government concerned and WHO. The length of the delay was usually determined by the time required to deliver the necessary vehicles, but also sometimes by a lag in the allocation of government funds for salaries. During this period, information regarding the past history of smallpox in the country was obtained, demographic data and maps were collected, and staff were selected and trained. As has already been noted, the compilation of the smallpox data available from state and provincial offices and other sources often revealed more cases than those recorded in statistical offices and officially reported to WHO. The compilation of such data made better baseline information available for use in deciding on priority areas for vaccination and in gauging subsequent progress. Except in areas in which malaria eradication programmes had been conducted, the existing maps were generally inaccurate and demographic data often at considerable variance with what programme operations later revealed. Nevertheless, such maps and data were useful as points of departure, changes being made in them as the programme progressed and additional information was obtained.

The supervisors and vaccinators for the programme were mainly health personnel who had previously been engaged in smallpox vaccination or who had been transferred from other field programmes, such as those for BCG vaccination or leprosy or yaws control, which for one reason or another had all but ceased operations. The numbers of health personnel required for the programme were not large and, because underutilization of health personnel in most endemic countries was common, it was seldom necessary for the government to hire additional staff to serve as vaccinators or supervisors. Those who served as vaccinators had usually had at least 6–8 years of education and were sufficiently literate to use forms for recording data. Illiterate vaccinators were also successfully used, especially after 1973, when the programmes were greatly intensified. Supervisors, in general, had had at least 10–12 years of education and had sometimes received additional training in the operation of health programmes.

For most smallpox eradication programmes, special training lasting 1–4 weeks served to familiarize the staff with the nature of the programme and with their duties and responsibilities. In all but the largest countries staff numbers were sufficiently small to permit close and continuous contact between the senior national staff, the field supervisors and the vaccinators, thus facilitating supervision and a progressive improvement in performance. In larger programmes, and where the staff were widely dispersed, supervision was more difficult and the programmes were generally less effective. During the course of the programme in India over the period 1974–1977, however, an effective method was found for the supervision of large numbers of widely dispersed staff (Brilliant, 1985). A 1-day meeting of senior staff and supervisors was held every month to review performance, progress, strategy and problems. Subsequently, the supervisors and junior supervisors held a similar 1-day meeting and, finally, junior supervisors and vaccinators reviewed the progress in an area served by a health centre. Although the national programme involved more than 100 000 workers, it proved feasible to supervise activities closely and to modify and continually redirect the programme effectively.

Special activities were undertaken to interest and involve health staff based in the outpatient departments of hospitals, in health centres and in similar facilities. In group meetings and during field travel, smallpox eradication programme staff regularly discussed with them the nature and objectives of the programme, emphasized the need to report smallpox cases, and provided supplies and instruction in the proper storage and use of freeze-dried vaccine. Experience showed, however, that in most countries such health staff failed to report cases regularly, usually vaccinated very few of those who attended clinics and seldom undertook to vaccinate people living in nearby houses or villages.

Provision was made for the cold storage of vaccine (at 0–4°C) in the capital city, sometimes in refrigerators belonging to the programme and sometimes in other units used for the refrigeration of meat or vegetables and fruit. Vaccine was also kept at state and district centres in ordinary refrigerators, which were often provided by the programme, the number and location depending on the difficulties of travel and the availability of transport. The distribution system was designed so that vaccine would not be exposed to ambient temperatures for more

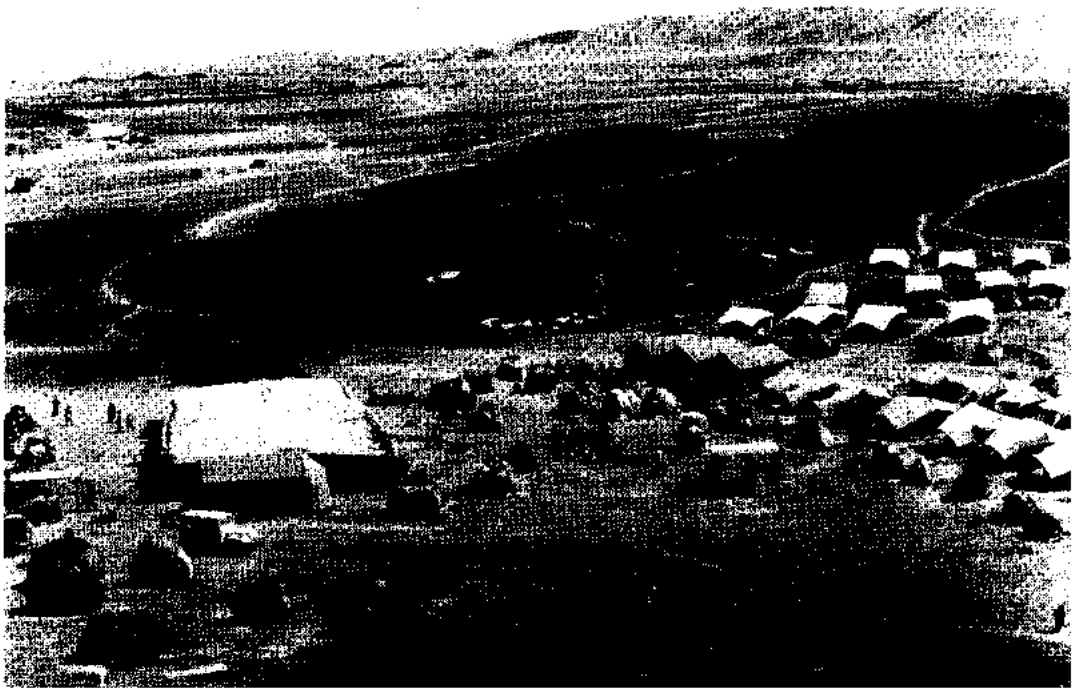


Plate 10.25. Refugee camp for Ethiopians in Djibouti. Special vaccination campaigns were regularly conducted in such camps to prevent outbreaks of smallpox.

than 30 days. In most programmes, however, the maintenance of an effective "cold chain" proved difficult and was often unsatisfactory, usually because of the mechanical failure of refrigerators, interruptions in electrical supply or lack of kerosene. Not infrequently, the vaccine was exposed to ambient temperatures for more than 30 days but because of the high titre and the stability of most vaccines, primary vaccinations were usually successful in 95% or more of the subjects concerned even when the vaccine had been exposed to such temperatures for as long as 6–9 months. Despite failures in the distribution system, unsuccessful vaccinations with properly manufactured vaccine were uncommon after 1967.

Special efforts were made to ensure that vaccination teams and health units always had on hand an adequate supply of vaccine and bifurcated needles. The instructions therefore called for orders to be submitted in advance so that supplies could be replenished well before they ran out, but the system rarely worked well; most units and many countries waited until supplies were exhausted before ordering more. The reserve supplies of vaccine and needles in Geneva, from which deliveries could be made within 48–72 hours, helped to overcome this difficulty.

Finally, health education materials, such as posters and brochures, radio messages and other media material, were prepared. Although these were used in all programmes, such studies as were done showed that individual discussions with villagers by team leaders, vaccinators or search workers were much more effective in obtaining cooperation and participation.

After the necessary equipment had been assembled and personnel recruited, pilot projects were conducted in most countries. Because mass vaccination was comparatively simple and often familiar, they seldom lasted more than a few weeks or months and were designed primarily for training purposes rather than to test alternative methodologies.

Execution of the mass campaigns

Most mass vaccination campaigns were designed to be completed during a period of 1–3 years, depending on the size of the country and the number of personnel available. Field activities usually began in areas with the greatest population density and the

highest smallpox prevalence, thereafter moving progressively to adjoining areas. In practice, it was found best to begin the campaign in an area in which vaccination was readily accepted by the population and the logistics were simplest, and to move to more difficult areas when operational systems were well established.

Most countries used mobile vaccination teams; they varied in size but usually consisted of 2–8 persons, each team being given a vehicle. For ease of supervision and supply and to economize in transport, groups of 4–8 teams usually worked in contiguous areas under the direction of a senior health supervisor. The teams usually worked without interruption for 3 weeks, followed by 7–10 days' rest. A useful tactic, but one seldom used, was for a team of 2–3 supervisors to move from area to area and to employ local health staff to assist them. Having individuals on the team who were familiar with the people and the area and who spoke the local language enabled better vaccination coverage to be achieved. Although wider use of this approach would have been desirable, the necessary cooperation of the local health staff was usually difficult to obtain.

If work continued throughout the year, 250 days of field work were possible, but 150–200 were more usual. In some Asian countries in particular, religious and national holidays were frequent and often prolonged; in others, effective field work during the seasonal rains or the hottest months was difficult, if not impossible.

Work schedules had to take a number of factors into account. Nomads, for example, were often widely dispersed during most of the year but would congregate at certain sites to graze their animals or to assist in the harvest during a comparatively brief period. In rural areas, farmers busy in the fields avoided vaccination for fear of the resulting fever and sore arm; better coverage was therefore achieved by vaccinating during slack periods in the agricultural calendar. Special programmes had to be scheduled to vaccinate people attending religious festivals, as in the Indian subcontinent and in many Muslim countries, where thousands or even millions of people often forgathered. Programmes for refugees and migrant seasonal workers were also important. The time of vaccination also had to be taken into account. If vaccination was offered, for example, from 9 o'clock in the morning to 5 o'clock in the afternoon, large numbers of persons were usually away from their villages—in the fields, at school or at markets. Vaccination in the early morning and in the evening resulted in better coverage but such a schedule was often difficult to arrange.

Two basic approaches to mass vaccination were employed. Throughout Africa and South America, the assembly-point system, in which many subjects for vaccination gathered at a designated site, was well accepted and therefore widely employed. In Asian countries, house-to-house visits were usually made by vaccinators, although large numbers of persons were sometimes vaccinated at places such as railway stations, ferry crossings and refugee camps.

Assembly-point vaccination. At an assembly point, many people could be vaccinated by a few vaccinators in a short time if the local leaders lent their support. That support was usually sought by an "advance man" attached to the mobile teams, who visited the area concerned one or more days before the team was to arrive in order to meet the leaders, explain the nature of the programme, and enlist their support in assembling the people and controlling the crowd.

Jet injectors had been expected to be of especial value in campaigns using the assembly-point method, but their potential was seldom realized. With very well organized assembly points 1000–1500 persons an hour could be vaccinated using a jet injector but it was difficult to assemble and to vaccinate so many persons for more than a few hours each day. Because the great majority of the population lived in small, widely scattered towns and villages, the travel of the teams and the preparations at each individual site took a good deal of time. In practice, a team of 2 vaccinators using jet injectors averaged only 1500–3000 vaccinations a day, much the same as the number performed by 3 vaccinators with the much simpler bifurcated needles. Thus, in most circumstances, bifurcated needles were preferred.

The assembly-point system was usually effective in obtaining coverage rates of 80% or more wherever local support was reasonably good and even higher rates when smallpox was known to be present in the area. In rural areas, the best coverage was obtained when the assembly points were so situated that no one had to walk more than 5 kilometres, and preferably no more than 2

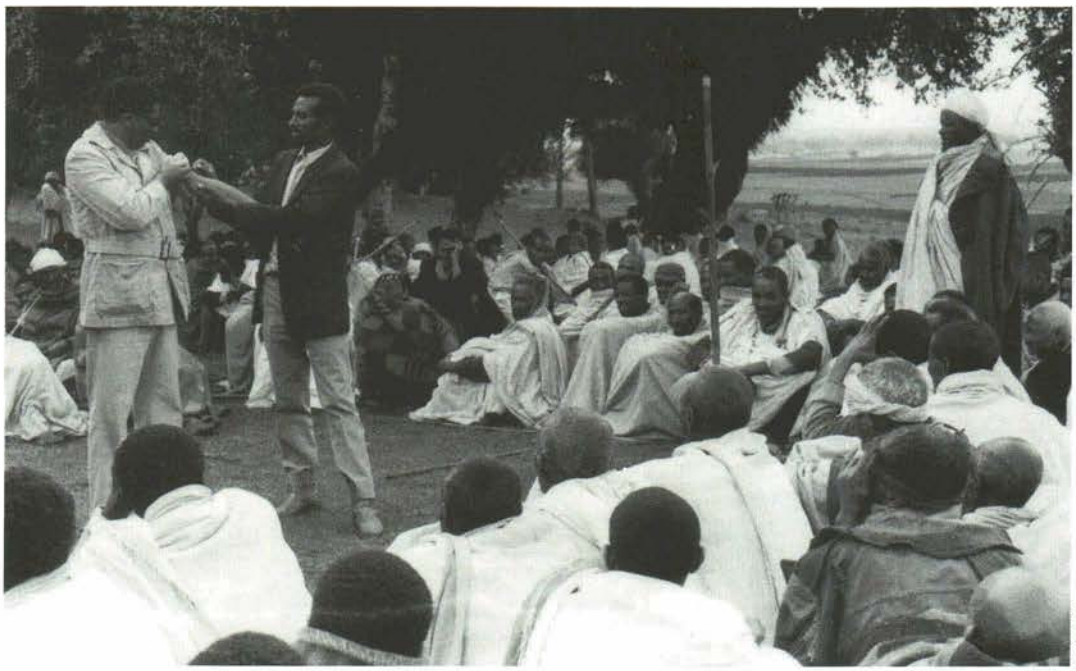


Plate 10.26. An "advance man" meets with village elders in Ethiopia to demonstrate vaccination and to explain the programme.

kilometres. Otherwise, many individuals were missed, especially children who were too young to walk very far or too old to be carried over long distances. In cities and towns, assembly points were much more closely spaced.

At the assembly points, police or village leaders were needed for crowd control, especially in areas in which the people were not accustomed to orderly queuing. Special measures also had to be taken to prevent the crowds from pressing in around the vaccinators to watch what they were doing. This was usually effected by arranging for the line of people to be vaccinated to pass through a building or between specially erected fences. The information recorded about each person vaccinated was kept to a minimum. Although some health authorities insisted initially on registering each individual by name, age, sex and place of residence, they soon discovered that this made the clerical task too burdensome and that the records compiled were of little or no value subsequently. A simple vaccination tally sheet (Plate 10.27) was commonly used to record the number of vaccinations performed by age group.

House-to-house vaccination. In most of the endemic countries of Asia, vaccinators customarily went from house to house, and this practice was continued throughout the programme. To many health officials, systematic and orderly house-to-house visits seemed more likely to ensure high levels of vaccination coverage than asking people to gather at assembly points. The method, however, had certain intrinsic drawbacks which generally resulted in a lower rate of coverage. Since fewer persons could be vaccinated in a day than at an assembly point, larger numbers of vaccinators were required. They were often more poorly paid, less strongly motivated and therefore less reliable than the assembly-point vaccinators. They were also widely dispersed, so that it was difficult to supervise them, or even to determine whether they had worked at all. The household members, since they did not know when the vaccinators were going to call, were often absent, and resistance to vaccination was more frequent when families were approached one by one in this manner than when they were part of a large crowd in the carnival type of atmosphere associated with the assembly-point method. During the global eradication programme, well-supervised house-to-house programmes were conducted in some high-risk areas of Asian countries, but were seldom assessed. In most areas, traditional practices continued, indivi-

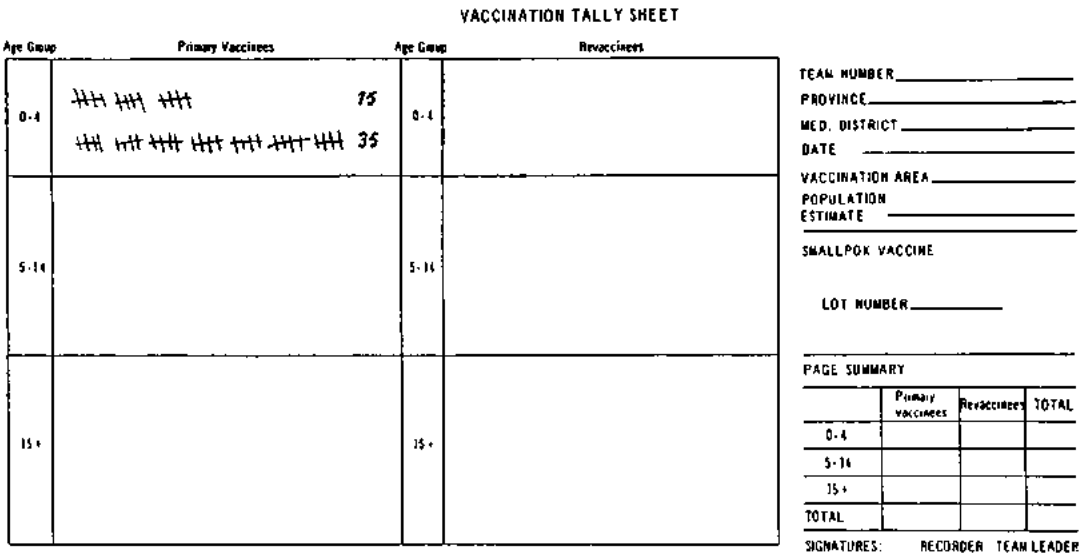


Plate 10.27. A vaccination tally sheet.

dual vaccinators being assigned responsibility for populations ranging from 5000 to 20 000 but seldom vaccinating more than 25–50 persons a day. As is described in Chapter 15, the system was costly for what it achieved.

Smallpox vaccination was generally well accepted throughout the world, even among many groups with little prior contact with health services. Groups which resisted vaccination tended to make the greatest impression on programme staff and their importance was magnified by virtue of the time and energy needed to vaccinate them. The older adults, especially women, often objected to vaccination on the grounds that they were already immune, which, in fact, most were. However, for a team trying to contain an outbreak and therefore to vaccinate everyone in the area, the older women in particular were a continual source of frustration. Some orthodox religious groups objected to vaccination on principle; on several occasions this resulted in outbreaks difficult to control. However, the numbers involved were seldom large and, through religious leaders and government officials, most people could eventually be persuaded to accept vaccination. Where variolation was practised, as in the mountainous areas of Afghanistan and Pakistan and in Benin, Togo and western Nigeria, variolators, as well as some members of the population, objected to or actually forbade vaccination. Except in the more remote areas of Pakistan, however, it was eventually possible to persuade most of them to accept it.

The largest group to resist vaccination were the Amharas of the highland plateau area of Ethiopia. To most Amharas, vaccination was unknown and neither religious leaders nor government officials were able to influence their attitudes significantly. Because only the mild variola minor form of smallpox was prevalent in the area, they did not fear the disease, even when outbreaks occurred. Many methods were used to enhance their acceptance, including that of providing drugs against other diseases after successful vaccination, but large numbers of people still refused. Fortunately, resistance was by no means universal and smallpox transmission gradually ceased in this widely dispersed population.

The simultaneous administration of one or more antigens in addition to smallpox vaccine was known to be both safe and efficacious as well as economical of transport and personnel. For this purpose, however, additional resources had to be made available for the programme and changes in operational procedures introduced. This proved possible in a number of control programmes. In

western and central Africa, measles vaccine was given to all children between 6 months and 4 years of age; in some programmes yellow fever vaccine was also given to persons of all ages; and in others, BCG vaccine was administered, usually to those aged 0–15 years. In many countries of eastern and southern Africa, both smallpox and BCG vaccines were given from the beginning of the programme and, in Afghanistan, diphtheria, pertussis and tetanus (DPT) vaccine and BCG vaccine began to be administered after smallpox transmission had been interrupted.

The question whether other vaccines might be given during the smallpox vaccination campaign did not arise in most countries, however. Up to the end of 1977, when the mass campaigns had concluded, few of the endemic countries routinely provided other vaccines because they lacked the foreign currency to buy them and little was contributed by international agencies. BCG vaccine, which UNICEF provided to a number of developing countries, was an exception. It was difficult, however, to conduct a programme for the administration of both BCG and smallpox vaccines, since the former was usually given by a more time-consuming method—intradermal injection using a syringe and needle. In Africa, vaccinators could routinely administer 500 or more smallpox vaccinations a day using bifurcated needles but only 100 or so BCG vaccinations. To give both vaccines together required either a substantial expansion in the size of the teams—difficult because of the limited transport available—or a much slower-paced programme and inevitably a delay in interrupting smallpox transmission.

To facilitate the development of combined smallpox–BCG vaccination programmes, the Smallpox Eradication unit in Geneva promoted studies of the feasibility of administering BCG vaccine with the bifurcated needle and with the jet injector. While the results obtained with the bifurcated needle were equivocal or poor, those with the jet injector were quite satisfactory. Where jet injectors were used—in Zaire and many countries of western and central Africa—the two vaccines were administered at the same time but inoculated into different arms. Except for the the constant difficulty of ensuring an adequate supply of BCG vaccine, these programmes generally functioned well.

Although an effective mass campaign for the simultaneous administration of different antigens was difficult to start, the feasibility increased as experience was gained and an administrative structure developed. It seemed logical and desirable to the WHO Smallpox Eradication unit to encourage the transformation of the programme, as smallpox began to be eliminated, into one for the provision of other antigens as well. DPT and poliomyelitis vaccines were the best candidates, as the diseases concerned posed problems in the developing countries and the vaccines were inexpensive and as yet little used. Donations of vaccine would, however, have been needed as well as additional staff at Headquarters to develop plans, mobilize resources and provide training. Efforts were made in 1970 and later to persuade senior WHO staff of the desirability of this approach, the importance of timely action increasing as one country after another became free of smallpox and began to dismantle its programme. There was, however, resistance to the development of what was seen as yet another "vertical" programme until 1974, when the Twenty-sixth World Health Assembly decided to establish the Expanded Programme on Immunization. By then, smallpox eradication had proceeded so quickly that a number of national vaccination programmes had ceased to function.

On balance, the mass vaccination campaigns were remarkably successful in most countries, high levels of acceptance and coverage being attained in almost all in 3–4 years or less. The campaigns cost most countries no more than they had been spending on their regular control measures. As the chapters on field operations will show (Chapters 12–22), the assembly-point system of vaccination did not require large numbers of national personnel and international support usually amounted to no more than US$0.07–0.25 per head of population over the course of the programme. The mass campaigns were, moreover, politically attractive, in some areas providing an important link between the people and the government—sometimes virtually the only one.

Maintenance vaccination by the health services

At the conclusion of their mass vaccination campaigns, most countries planned for continuing programmes of maintenance vaccination to be provided by the existing health services. Health units were requested to ensure the vaccination of newborn infants

and of children at health clinics and at school entry and to undertake periodic community-wide vaccination campaigns, but the outcome was seldom satisfactory. In all countries, large numbers of people visited health units daily for treatment but the opportunity was rarely taken to vaccinate them. When health centres were inspected, vaccine was regularly found which had been reconstituted days or even weeks previously and continued in use even though stored without refrigeration. Many of the vaccinations performed were probably unsuccessful but in few centres were subjects checked to see what the results had been.

After the mass campaigns, the levels of vaccinial immunity declined steadily in almost all countries, as was documented during surveys conducted for certification purposes. Although not the intention, this proved, paradoxically, to be helpful in the certification process; with large numbers of susceptible persons, smallpox, if present, was more likely to spread and to be detected than it would in a well-vaccinated population.

Assessment

The WHO Handbook called for "a programme of continuing evaluation of coverage and vaccination take rates by an assessment agent (or team) who is administratively independent of the vaccination team". What was envisaged was a random sample survey of 10–25% of those vaccinated, to be conducted 1–4 weeks after mass vaccination had been completed in an area. The use of an assessor who reported to someone other than the vaccination team leader increased confidence in the reliability of the findings. Although other useful types of evaluation were proposed in the WHO Handbook and were used subsequently in the programme, an ongoing appraisal of this type provided the most important information for use in the quality control of the campaigns. Like surveillance, however, sample assessment was unknown to most health officials and was adopted only with reluctance. Most considered it wasteful of manpower and vehicles to create a team whose sole responsibility was to check the work of others. Many were more willing to provide sufficient personnel to re-examine the entire population and vaccinate those without vaccination scars, but this was rarely feasible or cost-effective.

Independent assessment, although not universally practised, was used to good effect in assembly-point programmes in Brazil and in a number of African countries, as well as in the house-to-house vaccination campaign in Afghanistan. The rationale of the methods and standards deserves comment. For a reasonably accurate appraisal of the quality of work in an area to be made, a random selection of villages was important, however crudely done, otherwise the assessment teams would visit the villages that were most easily accessible by vehicle and therefore the most likely to have the best vaccination coverage. The methods used for random selection varied widely, from a sophisticated approach in Guinea, in which villages were selected within a defined sampling frame and in proportion to population, to a much simpler one in Afghanistan, in which pieces of paper bearing the names of villages in which vaccination had been performed were placed in a box and the specified number drawn at random. The method of sampling was less important, however, than the fact that sampling was done and that teams were aware that their work was regularly checked and that, if the results were unsatisfactory, more work would be required. Most took pride in being able to meet or surpass the established goals.

The assessment teams also evaluated the efficacy of the vaccine that had been used, but only in the case of primary vaccination. The primary vaccination lesion was so distinctive that there was never any question whether vaccination had or had not been successful. With revaccination, on the other hand, there were many equivocal responses among persons with partial immunity, and their interpretation differed from observer to observer. Moreover, a standard for successful revaccination was impossible to establish because of the varying levels of immunity in different areas. For primary vaccination, a successful take rate of at least 95% was established as a minimum standard, a figure which permitted a margin of error in recording and observation because take rates normally approached 100% when a satisfactory vaccine was properly applied. The assessment of results of primary vaccination only had the further advantage that the response could be evaluated 1–4 weeks after administration, rather than in the 6–8 day period required to evaluate revaccination responses. More flexible schedules for the assessment teams were thus possible. In all but a few instances, primary vaccination take rates consistently exceeded 95%; where they were found to be

lower, problems of vaccine handling or vaccine quality were usually discovered which could then be rectified.

Coverage after a campaign was measured in terms of the proportion of the population with a vaccination scar or with evidence of recent primary vaccination rather than in terms of the proportion vaccinated during the campaign. It was simpler and more reliable to inspect a person, particularly a child, for the presence or absence of a vaccination scar or lesion than to ask whether the subject had been vaccinated during the team's visit. This simplified method was feasible because vaccinial immunity was so durable in endemic areas, even after a single primary vaccination. The standard of performance originally set by the WHO Handbook was that not less than 80% of the population should show evidence of immunity, as indicated by a vaccination scar. In most programmes, levels of 90% or more were common, the highest rates being among adults and older children. With time the methodology was changed so that in most countries only children under 15 years or even under 5 years were examined, but the criterion was retained that not less than 80%, and sometimes 90%, of that age group should have a vaccination scar or lesion. This approach was operationally advantageous because children were more likely than adults to be found in or near their homes when a visit was conducted. Given that older age groups consistently had even higher levels of coverage than the younger ones, a standard requiring evidence of immunity in 80% of children effectively ensured an overall population immunity of more than 90%.

The assessment data provided information on performance, but they were also used to guide operations, which was just as important. When it was found that vaccination coverage was below standard, teams were usually required to return to the area, sometimes without the payment of travel allowances, to revaccinate the entire population.

Other forms of assessment were also employed in the mass vaccination campaigns. One, used almost everywhere, was to compare the number of vaccinations performed in an area with the estimated resident population. This provided a rough indication of the success of the campaign but an unreliable one because the available population data for small localities were often highly erroneous and often many non-residents were also vaccinated. In some areas of western Nigeria, for example, where the number of vaccinations reported to have been performed corresponded to 80% of the population, sample surveys later showed that fewer than 40% had vaccination scars.

Another approach was to enter the names of all residents and their vaccination status in a register (as in India) or on cards (as in Zaire), in the expectation that, after the vaccination team had left, health staff could refer to the records and vaccinate those who had been missed. The preparation of such records, however, was exceedingly time-consuming; keeping them up to date proved all but impossible; and the effort required to find and to vaccinate every person who had been missed was prohibitive. All countries which endeavoured to register the names of vaccinated subjects soon abandoned the practice as being impracticable except the United Republic of Tanzania. There, what were called "ten-cell chairmen" prepared a list of all the inhabitants of their assigned area and, when vaccination teams arrived, called individuals forward one by one for vaccination. There were few countries, however, in which political or other organizations could assume such a burden of clerical work, and even in the United Republic of Tanzania the information was not retained as a permanent record.

Sample surveys to assess the status of immunity of selected population groups were undertaken periodically in a number of programmes. Such surveys proved useful for deciding on vaccination strategies for special groups and, on a larger scale, were important when it came to certifying the absence of smallpox. National and other large-scale surveys were performed in western Africa and in India but they proved of little value. National and, in Nigeria, regional surveys, conducted in western Africa in 1969–1970 to measure overall programme performance, revealed problems in some areas, but the information was obtained so long after the campaign had been conducted that the specific causes of the problems could not be identified nor corrective measures taken (see Chapter 17). In India, the forms and assessment methodology used in Afghanistan (see Chapter 14, Plate 14.3) were introduced in some states. It was hoped that health officers responsible for the house-to-house vaccination campaign would identify areas and

populations which had not been well vaccinated and would take corrective action. Although tens of millions of people were examined in the course of assessment exercises, most health officers saw the activity as an end in itself and took no action to correct problems. Large-scale surveys of this kind were gradually abandoned.

Progress in national programmes had traditionally been measured by the numbers of vaccinations reported each year. The data, compiled by administrative units, continued to be collected throughout the course of the programme but varied considerably in quality. In most areas, the vaccinations actually performed were counted, but in some, the numbers reported were equivalent to the assigned goals, while in others, they were estimated on the basis of the quantity of vaccine used. As the programme progressed, these data received less and less attention and greater emphasis was placed on trends in the numbers of reported cases of smallpox. By the early 1970s, data on the numbers of vaccinations reported each year and in each country ceased to be compiled in Geneva and, by the mid-1970s, interest in them was largely confined to the media, which regularly inquired about the numbers of vaccinations being performed. It proved preferable to give the reporters some estimate than to attempt to explain why such data were no longer available.

Legislation

Legislation on smallpox and vaccination existed or was adopted in most countries, but in most instances it proved to be of little benefit other than as an official statement of policy. In the majority of countries, legislation was enacted which called for compulsory vaccination at or shortly after birth, periodic revaccination, and the mandatory isolation of patients; some countries prohibited variolation and required citizens to report cases of smallpox. On the few occasions when action was taken to enforce such laws, the results were poor and often counterproductive. In India, for example, attempts to levy fines on persons who refused to be vaccinated led to protracted proceedings in the courts without any apparent increase in compliance by the general public. The forcible isolation of patients in hospital often caused many families to hide infected household members and impeded effective containment measures. The prohibition of variolation may have caused some variolators to abandon the practice but in Afghanistan, for example, it resulted in the general public refusing to supply information about them, making it more difficult to identify them and to persuade them to cease their activities.

Other forms of coercion, however, were occasionally needed and effective in special circumstances. For example, in crowded refugee camps, the rule that all persons should be vaccinated before being given food ensured rapid and complete coverage; during containment vaccination, a police presence often discouraged resistance to vaccination; and in Botswana the government's threat to expel a religious group from the country secured cooperation in accepting vaccination when other measures had failed.

The Surveillance–Containment Strategy

The history and rationale of the surveillance–containment strategy have been described earlier, as has its implementation at the global level. At the national level, the foundation for implementing the strategy was the network of reporting posts making up the national reporting system, complemented by mechanisms for the prompt investigation of cases and the containment of outbreaks. The WHO Handbook stressed the importance of establishing or strengthening a reporting network from the inception of each national programme but postulated that, in countries with a high incidence of smallpox, the available resources would not immediately permit the investigation and containment of all outbreaks. Although the Handbook recommended that a reporting system should be established in all countries as soon as possible, it proposed that, in countries reporting more than 5 cases per 100 000 population, case investigation should be limited to major outbreaks and to those in areas in which mass vaccination had been completed. In other countries, all cases were expected to be investigated and containment measures taken. In mid-1967, the data available showed that only 13 of the 31 countries in which smallpox was then endemic had rates of 5 per 100 000 or more, of which 6 were in western Africa (Dahomey (Benin), Mali, Niger, Nigeria, Sierra Leone and Togo), 4 in eastern and southern Africa (Burundi, Uganda, United

Republic of Tanzania, and Zaire) and 3 in Asia (India, Indonesia and Pakistan).

The belief that it would be some time before all reported cases could be investigated and contained rested essentially on 3 premises which, in most of the endemic countries, proved to be incorrect. The first was the notion that the level of vaccinial immunity in the population was universally low, especially in countries with a high smallpox incidence, and that mass vaccination would be necessary before the numbers of cases decreased sufficiently to permit each to be investigated. Overall vaccinial immunity in some countries was indeed low and mass vaccination campaigns did serve to reduce incidence, notably in Afghanistan, Brazil, Ethiopia, Nepal, northern Nigeria and Sierra Leone. In 1967, however, half or more of the population of most countries were found to have vaccination scars, and among these countries were some which reported a substantial proportion of all cases. In India, Indonesia and Pakistan, more than three-quarters were already fully or partially immune because of past disease or prior vaccination. It was found there that the interruption of smallpox transmission was less closely related to an increase in the proportion of the total population with vaccinial immunity than to better reporting and containment measures. The second misconception was that, where smallpox incidence was high, cases would be so numerous and widely scattered that a great many teams would be required to investigate and contain the outbreaks. With few exceptions, it was discovered that smallpox cases, although far more numerous than reported, were clustered in comparatively small areas, so that relatively few surveillance teams were needed to investigate and contain them. Finally, it was believed that, in most countries, health units were so few and so scattered that reporting systems would have to be based primarily on reports from village leaders, teachers and the like, and that these systems would require considerable time and substantial manpower to establish. In fact, most countries, even many of the least developed in Africa, had a remarkably extensive network of health posts and far larger numbers of health personnel than the WHO Smallpox Eradication unit had expected.

Soon after the Intensified Programme began, it became apparent that surveillance–containment programmes could be developed reasonably quickly and that such systems could rapidly interrupt transmission. The findings in East and West Pakistan in the years 1965–1968, in eastern Nigeria in 1967 and in Tamil Nadu State (India) in 1968 showed that:

(1) The reporting of cases, although incomplete, was usually adequate to identify most large outbreaks; many other cases could be readily discovered by a few field teams through the investigation of reported cases and by questioning health staff and villagers.

(2) Patients with smallpox usually transmitted the disease to very few people and only to those in close face-to-face contact. Transmission in markets or schools, for example, was uncommon. Outbreaks therefore tended to be clustered among acquaintances in certain parts of a city or areas of the country rather than being widely and randomly dispersed.

(3) Only persons with a rash were able to transmit infection to others; this made it comparatively simple to trace the chain of transmission from person to person.

(4) Where, as was the case in most countries, there was significant seasonal fluctuation in smallpox incidence, few persons or villages were infected during the season when transmission was at a low level; the discovery and containment of outbreaks during this season substantially reduced the number of cases in the subsequent smallpox season.

(5) Outbreaks could be easily and rapidly contained in most areas with a high degree of success by isolating the patient and vaccinating contacts and most persons in the immediate vicinity.

Given also that smallpox was so distinctive that it could be diagnosed reasonably accurately by villagers themselves, that there was an incubation period of fully 10–12 days between cases, and that the vaccine provided more durable protection than had been believed, the conditions for an effective surveillance–containment programme were unusually favourable.

Nevertheless, however logical and attractive the surveillance–containment strategy appeared to be, it was not readily accepted by programme directors. In part, the difficulty lay in understanding and accepting what seemed to be a simple concept—that all cases of smallpox were links in an identifiable continuing chain of infection and that, in every area, there was a finite, usually small

Plate 10.28. Careful questioning of villagers could usually reveal the source of infection of the first case in an outbreak of smallpox, but it was not always easy to tell from their directions where and how far away the person concerned might be.

number of chains. If a 2-week interval between cases is assumed, a single chain of transmission in a country would result in not less than 25–50 related cases in the course of a year. Even in countries with many cases, the number of chains of infection would not be large; a country with 500 cases a year would have no more than 10–20 such chains. Because the cases were so closely related to one another, the strategy required not only the containment of each outbreak but also the discovery of the antecedent cases and outbreaks in the chain and their containment. The lack of comprehension of this principle during the early years of the programme was indicated by the frequent reference by many programme directors to the occurrence of "sporadic" cases rather than to cases whose source of infection could not be found.

At the outset it was difficult to convince the authorities of the usefulness of setting up surveillance teams staffed by competent senior health personnel, although many created "fire-fighting teams" of poorly supervised vaccinators whose task was to administer vaccine when epidemics were discovered. Even when demonstration programmes were conducted by its most enthusiastic proponents, the surveillance–containment strategy was slow to gain acceptance. In western and central Africa, Dr William Foege and his colleagues tried to introduce it from the summer of 1968 but, as is recounted in Chapter 17, northern Nigeria, the most heavily infected area, did not participate. In 1968 and 1969, Dr A. R. Rao enthusiastically described his successful experience in interrupting transmission in Tamil Nadu State (see Chapter 15), but he did not succeed in persuading other state programme directors in India to follow his example; in Brazil, the achievements in 1969 of Dr Ciro de Quadros and his colleagues were likewise disregarded (see Chapter 12). Precisely when country-wide surveillance–containment programmes were fully implemented is difficult to say, but approximations are possible for the most populous countries. In the endemic countries, the first were those in western and central Africa, which began late in 1968. These were followed by Afghanistan and Indonesia in 1969, East Pakistan in 1970, Brazil, Ethiopia and Zaire in 1971, Botswana and the Sudan in 1972, India, Nepal and Pakistan in 1973, and Somalia in 1977.

Before 1973, simple surveillance–containment measures were employed, and these are described first in the following sections. From 1973 onwards, with global eradication closer and more resources available, the techniques became increasingly sophisticated; that period is discussed later in this chapter.

Routine notification of cases

The foundation of the surveillance system was a weekly report from each health unit which documented the number of smallpox cases seen that week; if none was found, a report showing "nil" had to be sent. To simplify and encourage reporting, only the most basic facts about the patients were requested: name, age, sex, village (or urban district), date of onset of rash, and whether the patient had previously been successfully vaccinated (as shown by the presence of a scar). The information could be contained in one line on a form and the report was therefore termed a "line listing of cases". These reports were to be dispatched at the end of the week to an intermediate administrative

unit (a state or province in smaller countries, a district in larger ones) and so on up the echelons, eventually reaching the national programme office. Each week, the national office reported to WHO Headquarters by telex or by mail the number of cases of smallpox by week of report and by district and state or province.

The system was designed to provide only the information that was relevant to programme operation at each administrative level. To check that the system was operating correctly, all units at each administrative level were expected to submit a report whether or not cases of smallpox had been detected. Numbers of deaths were not requested because progress in the programme was monitored in terms of smallpox incidence; the action to be taken, such as investigation and containment, was related to the occurrence of cases rather than of deaths. The information provided by the line listing, which was necessary for the investigation of cases by the surveillance teams, was of the greatest value at state or provincial offices in smaller countries or district offices in the larger ones. To facilitate the transmission of data by telegram or telex, higher-level administrative authorities received current data only on the numbers of cases by administrative unit. More detailed epidemiological information was usually collected and analysed nationally, but at a later stage.

In the notification system, all cases, irrespective of date of onset, were supposed to be recorded according to the week in which they were detected. In most countries, this meant the week in which they were seen by the health unit. A record system of this type was simple to operate and worked far better than one in which an attempt was made to record and tabulate all cases according to week of onset of illness.

In 1967, reporting practices varied widely from country to country; none followed precisely the pattern described above, but many had a reporting structure by which each health unit provided some sort of report weekly or monthly. This often entailed notifying cases of 25–50 diseases together with a variety of data on the operations of the health units. The reports were seldom used for operational or supervisory purposes and efforts were rarely made to ensure that they were submitted promptly or even that all units reported. At intermediate administrative levels, the situation was little different. Special notification systems were sometimes prescribed for the diseases subject to international quarantine regulations, such as smallpox. Some required village leaders and others who became aware of a case of the disease to report it to the responsible administrative authorities, but this was seldom done. Telex or telephone notification of the quarantinable diseases to national or provincial authorities was also requested in some countries but, again, not consistently carried out. With smallpox, there were other problems. Some health units diagnosed mild cases as "variola minor", considering them not to be "true smallpox", and did not report them. Where, as in India, the occurrence of cases was taken as evidence by supervisors that the vaccination campaign had been inadequate, health units suppressed reports of cases. In all countries, there was such substantial underreporting that it is not surprising that many countries believed smallpox to be a much less serious problem than it was.

The development of fully satisfactory notification networks took not less than 1–2 years. In many countries, this was facilitated by epidemiologists or mobile surveillance teams, each of which could usually cover an administrative area with a population of 5–10 million. The teams regularly visited each health unit to explain the programme, emphasize the need to report cases, encourage vaccination, distribute forms and vaccine, and check on late reporting. When cases were reported, the team investigated and contained the outbreaks, sometimes with the help of those at the health unit, and usually discovered many additional cases in the process. The frequent visits to the health units by the mobile teams and their prompt response when cases were reported proved to be a great stimulus to reporting, especially because other supervisory health staff rarely visited health units. Interest was also stimulated by national surveillance reports, published weekly or monthly in many countries and distributed to health staff at all levels.

Of the many problems encountered in developing the notification network, two deserve mention because of their relevance to the development of systems for other diseases. The first was the difficulty of persuading health authorities of the need to receive regular weekly reports, even when no cases were found. Most assumed that if no report was received, no cases had been detected. Experience showed, however, that the units

that failed to submit reports were usually the least effective in performing functions of all types, including vaccination. It was in such areas that large, hitherto unknown epidemics were the most frequently discovered. The second problem, encountered only in India, related to the decision by government authorities to record all cases according to week of onset rather than week of report. This resulted in chaotic record-keeping at all levels of the health system and contributed to a significant underreporting of cases (see Chapter 15).

Reporting units, even in the smallest countries, numbered 100 or more, and in countries with large populations, more than 1000. In India, the largest of the endemic countries, there were no fewer than 8167 units reporting weekly to 397 district offices, which, in turn, reported to 31 state programme offices, and these to the national programme office in New Delhi.

Other mechanisms for case detection

Routine case notification by health units, however assiduous, provided only incomplete data on numbers of cases. While such data were useful when deciding on the allocation of resources and as a point of departure for field investigations, additional measures were required to detect most and eventually all existing cases. For various reasons, patients did not always go to health units: some lived too far away; many, especially with variola minor, were not sufficiently ill to seek medical attention; some believed, rightly, that therapy would be of little value; and some wished to avoid detection so as to escape, for religious or cultural reasons, compulsory hospitalization or vaccination of household contacts. Not surprisingly, few patients came to health units in areas in which their dwellings were burnt as a prophylactic measure.

Help in detecting cases was sought from other health staff as well as from the government and private individuals. Health workers who moved from village to village in the course of family planning, malaria, leprosy or yaws control programmes should have been a useful source of information, but few contributed significantly until a reward was offered for detecting cases of smallpox. At different times and in different countries, appeals to report suspected smallpox cases were also made to administrative officials, religious leaders, development officers, agricultural extension workers and police and security forces; although many were helpful in other ways, their assistance in reporting on smallpox was minimal.

The most effective mechanism for detecting cases not seen at health units was the field investigation of the cases which had been reported. This was usually one of the first measures to be undertaken as surveillance programmes developed. Because the spread of smallpox tended to be limited to close personal contacts, many additional cases could usually be quickly discovered among the family and village or neighbourhood contacts of a case. By careful questioning of the patients, sources of infection in other villages could be identified and investigated. In Brazil, for example, the investigation of each reported case brought to light an average of 50 other cases.

As the Intensified Smallpox Eradication Programme progressed, it became apparent that the discovery of cases through routine reporting and the investigation of outbreaks were still inadequate. Many outbreaks were large by the time they were found and had already spread to other areas. Monthly or semi-monthly visits to all villages would have served to detect cases earlier, but in most countries it would have taken a year or more to visit every village, even briefly, given the number of the smallpox eradication staff.

Methods were therefore required to permit the staff to search rapidly for cases over wide areas. Among the first of the methods developed were inquiries by workers in schools and markets. Schoolchildren proved to be an exceptionally good source of information, being well informed as to who in their villages was ill and with what diseases and tending to be more forthcoming with information than adults. Surveillance teams were able, in a brief visit to a school, to question children from villages as distant as 5–10 kilometres. This approach, developed in Indonesia in 1969 (see Chapter 13), eventually became standard practice in all surveillance programmes. Akin to this approach was the questioning of those attending weekly markets.

When the numbers of outbreaks in a country or area decreased to very low levels, it became possible to search for cases among those who had been exposed to patients but had left the area. Tracing such contacts was difficult and not especially productive: com-

paratively few contacts became ill, since many were already immune or had not been sufficiently exposed to become infected. This technique was seldom used, therefore, even when there were few outbreaks.

The techniques for case detection described above were adequate for programmes in most countries of Africa and South America as well as some in Asia, but in the densely populated areas of Asia additional measures were adopted. Village-by-village and even house-to-house search became possible when additional staff could be recruited. The first village-by-village search was conducted in Indonesia in 1969 and the technique was employed thereafter in high-risk areas (see Chapter 13). It began to be used in India in 1972 and was extended nationally in 1973 (see Chapter 15). It then became the standard practice in the remaining endemic countries.

Data analysis and surveillance reports

Important elements of the surveillance process, as described in the WHO Handbook, were "the concurrent analysis and interpretation of reported data and studies" and the "widespread dissemination of the compiled and interpreted data to principal reporting sources and to others concerned with disease control activities". Although such activities might appear to be logical and routine in any systematic data collection process, they were uncommon at first in the endemic countries. This reflected, in part, the fact that progress in smallpox programmes had been measured by numbers of reported vaccinations rather than by numbers of cases of smallpox, and, in part, the disdain commonly felt by health officials for routinely collected morbidity data, which are everywhere recognized to be incomplete. Rather than using the information that was available, while at the same time trying to improve the system, such officials took little notice of the data.

Routinely collected morbidity data, incomplete and biased though they may have been, proved of value from the beginning of the programme and, as they improved, became ever more useful. Vaccination campaigns in most countries began in the areas that reported the largest number of cases and, in some, smallpox was eliminated before the national campaign came to an end. When cases were found primarily among children less than 15 years of age, the campaign strategy was altered to focus particularly on the vaccination of children. The early observation that most cases of smallpox occurred among persons who had never been vaccinated led to the studies previously mentioned which showed that vaccinial immunity was far more long-lasting than had been appreciated and to a consequent emphasis on primary vaccination. Many other illustrations of the usefulness of morbidity data could be offered.

In addition to the international surveillance reports, already described, national surveillance reports were also prepared and had a major impact on the various programmes. The first of these was a weekly mimeographed report, which was started in Brazil in 1967 (see Chapter 12). When special surveillance teams began discovering large numbers of unreported cases, it described what appeared to be a developing epidemic and this in turn attracted the attention of the press together with renewed political commitment and increased resources.

Containment

The containment of an outbreak was, in principle, straightforward, calling for isolation of the patient, vaccination of the members of his household and other contacts, investigations to determine if there were other cases in the area and identification of the source of the outbreak so that it, too, could be investigated and contained.

Before 1967, the responsibility for, and the methods used in, investigating and containing outbreaks differed from country to country. In most, local health officers were expected to initiate the necessary control measures, although national vaccination teams were sometimes deployed. Where variola major was present, mass vaccination was widely used when large outbreaks occurred, but smaller outbreaks were usually ignored. Special measures were seldom taken against the mild variola minor form. Patients usually remained in their homes or, where hospitals existed, were confined to a smallpox ward or a general infectious diseases ward. Special investigations to identify all cases or to determine the source of infection were practically unknown. If the patient recovered, it was sometimes the practice to disinfect surfaces in the room by scrubbing them with a formalin solution or carbolic soap and to burn the patient's clothing and bedding. In some places the practice was to

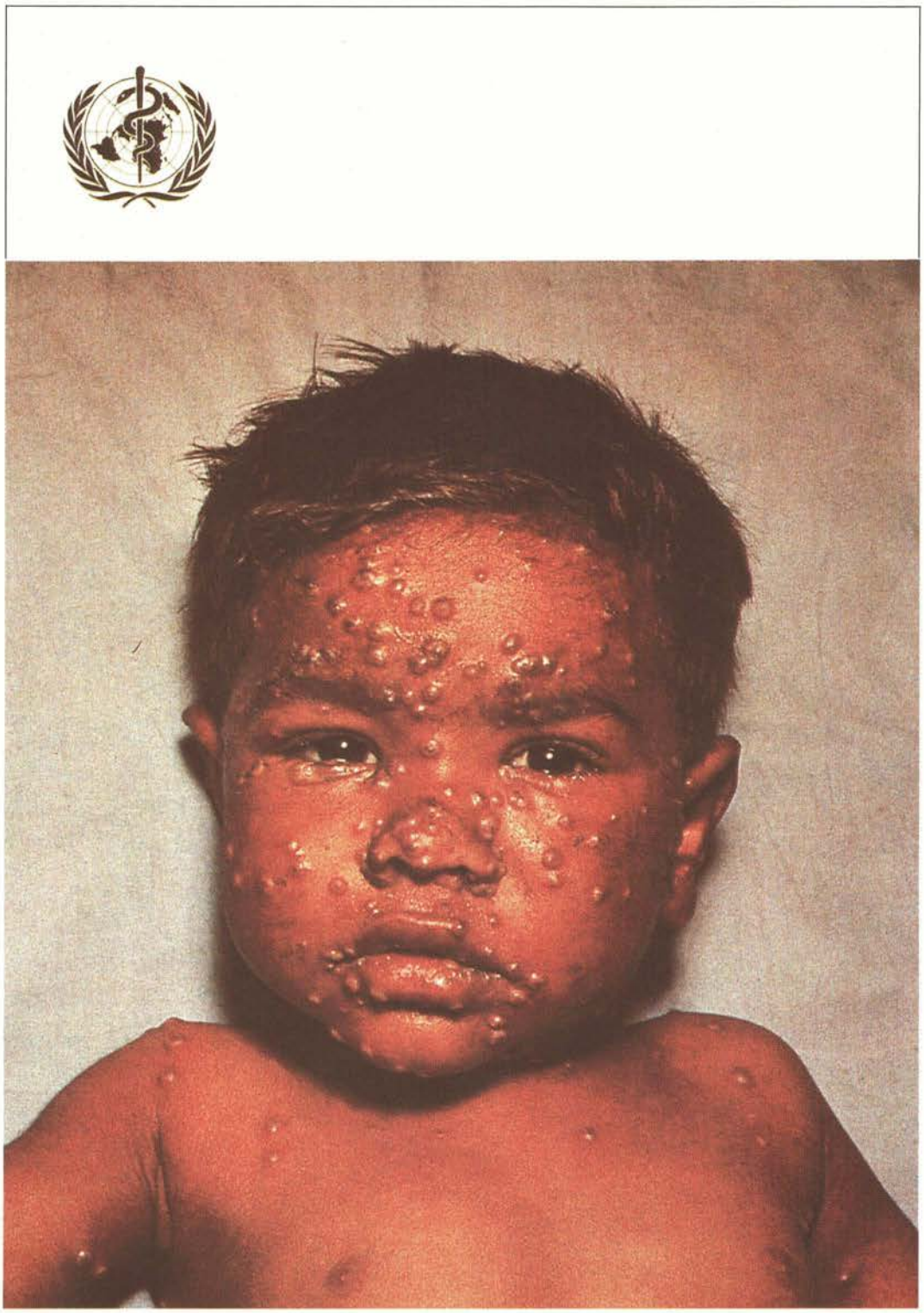


Plate 10.29. Front of the WHO smallpox recognition card that was widely used from 1971 in endemic countries. Smallpox eradication workers searching for cases would show the card and inquire whether anyone had seen a person with a similar rash.

Plate 10.30. Reverse of the WHO smallpox recognition card. It was on heavy-duty A4-size paper and cased in plastic for protection, unlike the pocket-sized version shown in Plate 10.11. In Ethiopia, a variant was used that showed an Ethiopian patient with variola minor.

Plate 10.31. Schoolchildren in Somalia (**A**) and in India (**B**) are shown the WHO smallpox recognition card and asked if they know of cases. Information about possible cases within a radius of 10 kilometres or more was frequently obtained in this way.

burn all dwellings in which cases had occurred.

The WHO Handbook devoted only 7 pages to a discussion of proposed containment and disinfection methods; the latter, quoted from Dixon (1962), were impracticable and, indeed, scientifically questionable. For example: "Letters: (*a*) Iron separate pages, both sides; (*b*) Expose loose pages and envelope to formalin vapour for three hours, then seal." The Handbook recommended that, in countries reporting fewer than 5 cases per 100 000 population, responsibility for containment should be given to a "knowledgeable person", defined as a trained epidemiologist. It recommended that the patient should be isolated, the source of infection identified, and household contacts vaccinated as well as "several hundred to several thousand persons ... in a brief intensive effort". It had little to say about the practical problems of containment, since there was little information in the published literature and those responsible for writing it had no practical experience of their own.

The diligence with which the containment of outbreaks was pursued after 1967 paralleled, in general, the development of reporting systems. Experience in executing containment measures gradually accrued as the programme progressed, but up to the end of 1973 the measures taken were comparatively simple ones, quite different from the disciplined methodology which began to be applied during the concluding stages of the programme in Asia and Africa in 1974.

Field experience showed that the isolation of patients in their own home or in a separate dwelling was usually the best practice. Because there was no effective therapy for smallpox, the hospitalization of patients was of little benefit. Moreover, hospitalized patients frequently spread infection to other patients, visitors and staff because hospital administrations regularly ignored isolation procedures. In fact, the authors are unaware of any institution in any endemic country, except one hospital in Madras (India), in which proper isolation practices were followed until they were introduced by smallpox eradication programme staff. So prevalent was the problem that programme staff often referred to hospitals as "smallpox transmission hospitals". Precautionary procedures were comparatively simple—the vaccination of staff and visitors, the isolation of all smallpox patients in a special ward and the vaccination of all such patients to protect any who might have been misdiagnosed. In most hospitals, however, smallpox patients were regularly accommodated in infectious disease wards with patients with other diseases or, at best, intermingled with chickenpox patients. Visitors usually came and went as they pleased and hospital staff themselves were frequently unvaccinated. Even late in the course of

Plate 10.32. Search workers used loud hailers at weekly markets, such as this one in Ethiopia, to seek information about possible cases of smallpox.

national programmes, infection in hospitals continued to occur, the last cases in Brazil and South Africa, for example, having been infected in this way. Indeed, the last case of endemic smallpox, in 1977, was in an unvaccinated hospital employee.

In most countries, the isolation of the patient in his home was both traditional and satisfactory but, in some, social customs led to the infection of many susceptible persons. Among some groups in the Indian subcontinent, for example, it was traditional for relatives and friends to visit those who were very sick, and in Indonesia young children with smallpox were often carried from house to house to be seen and comforted by relatives. Not surprisingly, simple containment measures were ineffective in these areas and smallpox spread rapidly. Interestingly, the most effective practices of patient isolation were found among scattered, illiterate African and Asian tribal peoples, who often arranged for the patient to be housed in a separate dwelling and to be cared for by someone who had previously had smallpox.

Special disinfection procedures after the patient had recovered were uncommon except for boiling or burning the patient's clothing and bedding; hospital rooms were cleaned in the ordinary way. Because few cases appeared to result from contact with fomites, no attempt was made during the programme to alter customary disinfection methods whatever they were.

The vaccination of contacts and the "several hundred to several thousand persons" in the area was fairly perfunctory until the programme was greatly intensified in 1974. Such vaccination was usually conducted during the main part of the day in the course of outbreak investigation. Inevitably, a number of residents, including household contacts, were away from home or their village at this time and so remained unvaccinated. Nevertheless, in Africa and South America, this brief but incomplete vaccination effort was usually sufficient to contain the outbreak eventually, even though one or several generations of cases might subsequently occur. In some countries, as cases became fewer, teams began to vaccinate early in the morning and in the evening to ensure more complete coverage, but seldom was a systematic effort made to enumerate and vaccinate all residents.

Attempts to trace the source of infection were sometimes made but were not always successful, special skills and diligence being required in questioning the patient, his family and friends. It was especially difficult to obtain such information, for example, from persons engaged in illicit activities such as smuggling or from people who had acquired the disease from prostitutes. A few programme staff, however, acquired an unusual mastery of the technique of tracing sources of infection and prided themselves on being able to identify the source of every

outbreak. Conversely, there were some otherwise competent epidemiologists who were consistently unsuccessful in this task; a few, especially early in the programme, simply characterized most cases as "sporadic".

Surveillance and Containment Measures after September 1973

From September 1973, the nature of surveillance and later of containment measures began to change significantly. By then, comparatively simple surveillance–containment operations and mass vaccination campaigns had been successful in stopping transmission in all but 5 countries—Bangladesh, Ethiopia, India, Nepal and Pakistan. Even in these countries, simple surveillance–containment measures had successfully eliminated smallpox from large areas, including much of southern India, Nepal and Bangladesh. Lack of progress in northern India and Pakistan, however, made it clear that neither country was likely to stop transmission without a more concerted effort. In the summer of 1973, therefore, a more elaborate system for case detection and subsequently for containment was devised by WHO and Indian staff which would involve large numbers of health service personnel, larger numbers of WHO and Indian epidemiologists, and greater financial support. Similar intensified efforts began late in 1973 in Pakistan, early in 1975 in Bangladesh, towards the end of 1975 in Ethiopia, and in May 1977 in Somalia when smallpox again became endemic there following importations.

Surveillance

In India, the persistence of smallpox despite high levels of vaccinial immunity was attributed partly to the high population density and partly to the frequent suppression of reports of cases by health staff. When, in 1974, the sources of all outbreaks began to be more carefully investigated, it became apparent that there was a third factor of significance—the frequent spread of smallpox over long distances. Of 6227 outbreaks for which the source was identified in 1974–1975, 1129 (18%) were found to have originated outside the state in which the outbreak had occurred and 25 outside the country itself (Basu et al., 1979). By comparison, data from Ethiopia, fairly typical of the experience in Africa, showed that the source of only 2% of outbreaks was outside the region (province) concerned (Tekeste et al., 1984).

It was believed that the key to eradication in the remaining affected areas was the more complete and the more prompt detection of outbreaks. Accordingly, it was decided to supplement the routine notification system by enlisting the participation of health staff from other programmes in national village-by-village, and eventually house-to-house, searches. Such searches had been shown to be effective in a district and in one state of India during 1972–1973 and, since large numbers of health staff were available in that country, it seemed reasonable to try to undertake them on a national scale. A detailed plan and guide were prepared which called for every inhabited locality in the search area to be visited in order to detect cases or to confirm their absence. In concept the plan was simple. The health staff in each administrative area would each be assigned 1–3 villages to visit each day. With the numbers available, an entire state could be covered within 7–10 days. After the search, the staff of the smallpox eradication programme, assisted by the local health workers, would contain the outbreaks which had been detected.

This proved to be feasible in Pakistan and Bangladesh as well as in India, but in Ethiopia and Somalia, with few health staff, temporary workers were required. Those from local ethnic groups, even the illiterate, who knew the topography and the people, proved to be the most effective—indeed, better than educated persons from urban areas. Considerable numbers were involved in each national search—more than 120 000 in India, 10 000–20 000 each in Bangladesh and Pakistan, and several thousands in Ethiopia and Somalia.

Training and motivating the large numbers of people involved were easier than had been expected. Training sessions of 1–2 days' duration were conducted before each search for personnel at the highest and intermediate administrative levels; subsequent sessions were conducted by intermediate-level supervisors for primary health centre supervisors, and, finally, by these supervisors for all health centre staff. Each intermediate and lower-level supervisor thus attended 2 training sessions, one as a participant and one as an instructor. At each meeting, the method of search was described

and, before the second and subsequent searches, the results and problems of the previous search were reviewed. The forms used were so designed that, when properly filled out, they guided each supervisor and search worker in carrying out his responsibilities.

The searches were conducted at different intervals in different areas—usually once every 4–8 weeks in endemic areas and once every 2–3 months in non-endemic areas. In the interval, additional search programmes were carried out in high-risk areas and in areas in which performance had been poor.

The development of a local search plan, in an area with perhaps 100 000–200 000 inhabitants, was the responsibility of the health officer in charge of that area. He selected the personnel to be employed and, using maps and demographic data, gave each worker 1–3 villages to visit each day on certain specified days. Those conducting the search travelled on foot or by bicycle. Some overlap in the sectors assigned helped to ensure that no areas were omitted. Usually, the workers travelled alone but in geographically difficult or dangerous areas a 2-man search team was used. A supervisor oversaw the work of 5–10 workers.

Through 1974, searches were conducted only in India and Pakistan and, until the autumn of that year, search workers were instructed to contact a number of different persons and groups in each village: the administrative head, postman, watchman and other local figures; people working in health units; children and teachers in schools; owners and customers of tea-shops; frequenters of markets; and persons at temples, mosques, churches, bus stops and similar places where people gathered in large numbers. The inhabitants of clusters of houses in each of 4 sectors of a village were to be visited, as were those in the poorest area. Although the more diligent workers were able to carry out all these activities, many did so perfunctorily, with the result that a number of cases failed to be detected. Overall assessment of the activities proved difficult, as did the identification of those performing inadequately. In the autumn of 1974, the numbers of cases and outbreaks had decreased sufficiently so that the method of search could be changed to one of house-to-house visits. A reward was offered and each search worker was required to place a poster or to paint a notice publicizing the reward on every tenth house, as well as on the schoolhouse. The quantity of forms, reports and posters required for each national search was considerable, one estimate in India indicating the need for a total of 8 tonnes of paper.

To ensure that the proper questions were asked, each search worker was trained to use a particular approach: he was to introduce himself as a health worker, explain the reason for his visit, show the WHO smallpox recognition card, inquire about suspected smallpox cases and tell the people about the reward and where to report suspected cases.

When a suspected case of smallpox was found, the search worker immediately notified his supervisor or the nearest health unit so that a containment team could begin work. In Ethiopia and Somalia, in which the population was widely scattered, search workers usually carried vaccine and were instructed to begin containment vaccination when a suspected case was found. The periodic discovery of suspected cases was important in sustaining the interest of the workers, but in areas which had become smallpox-free, interest was sustained and a mechanism of assessment provided by requiring them also to look for cases of chickenpox and measles and to detect and report all deaths accompanied by skin rash. This also provided added assurance that smallpox had not returned.

Special searches had to be devised for Somalia and other areas such as the Ogaden desert in which groups of nomads were

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Plate 10.33. Checking a bus station in Chotanagpur, India, for cases of smallpox. Regular checks of travellers by surveillance teams provided information about possible outbreaks over a wide area.

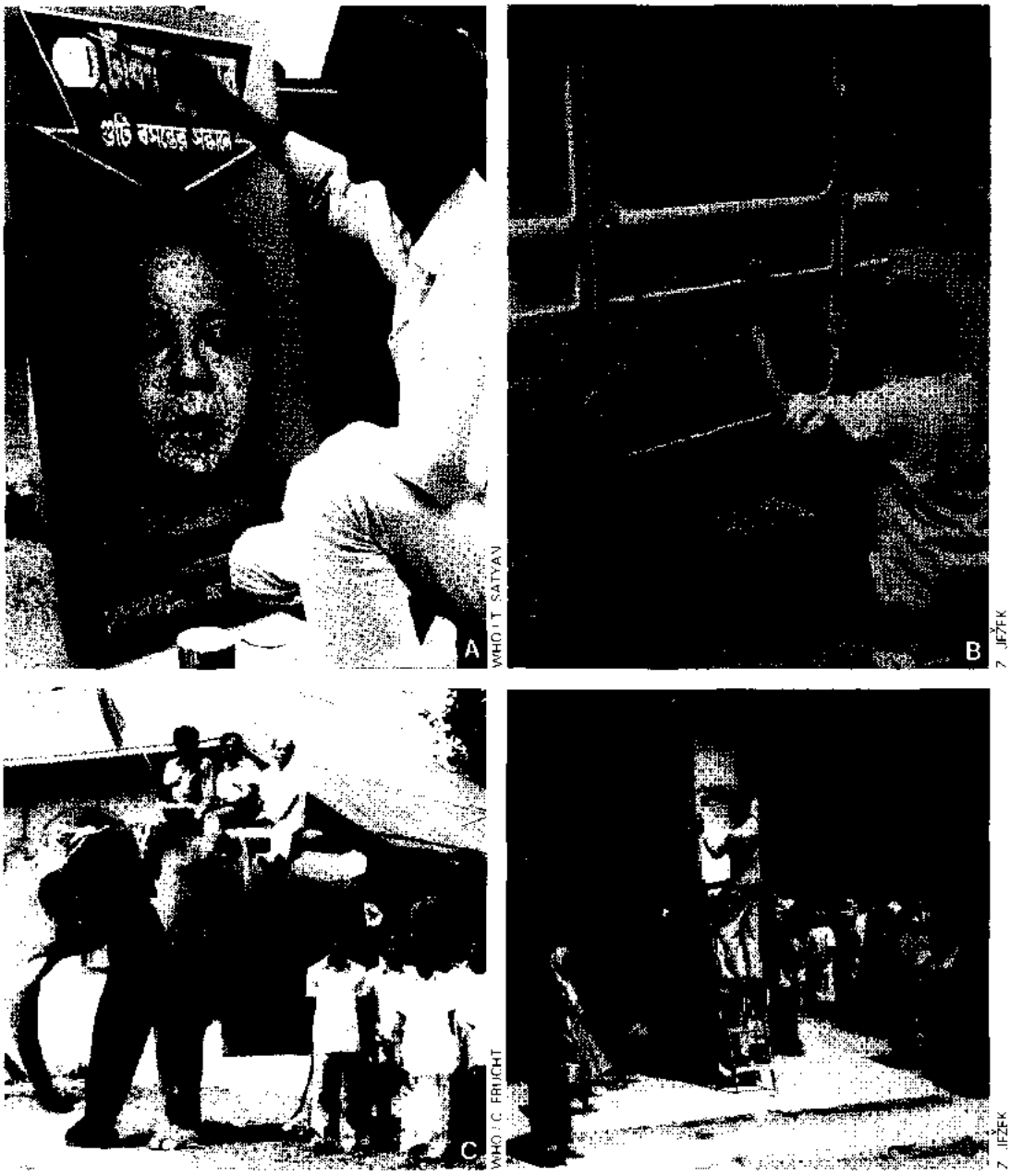

Plate 10.34. Publicizing the reward for reporting a case of smallpox. **A:** Repainting a poster in Bangladesh to show an increase in the amount of the reward. **B:** Painting a reward notice on a vehicle in Kashmir, India. **C:** Advertising the reward on an elephant in Assam, India. **D:** Hanging a reward poster in Somalia.

continually on the move. As is described in Chapter 22, different approaches were used to ensure the coverage of large areas while at the same time ensuring adequate supervision and assessment. In these areas, teams of 2 regularly walked long distances—50–150 kilometres—usually carrying vaccine so as to vaccinate any nomads encountered.

The organization of searches in urban areas was complex, and ingenuity was needed to coordinate the activities of the many and varied groups who usually participated, including numerous categories of municipal health staff and sometimes medical students, trainee nurses and volunteers from public services.

An intensive publicity campaign before and during the search, including the use of loudspeakers on cars and rickshaws, slides for projection, radio announcements, newspaper articles, handbills and posters, was found to be important in obtaining cooperation. As in rural areas, house-to-house searches were conducted, but schools, markets, factories and private medical practitioners were also visited. Special attention was given to areas in which migrants lived and to poor neighbourhoods. In urban areas, it was found that a search worker could visit 150 houses a day or about 1000 houses a week; 10 search workers with 2 supervisors were required to search an urban area with a population of 150 000.

Continuing assessment of search operations was as important as independent assessment of mass vaccination campaigns, as became apparent after the first search in India. Supervisors reported that 90% of villages had been searched and, indeed, thousands of previously unreported cases were detected, but a separate assessment by surveillance teams discovered that less than half the total had, in fact, been covered. An assessment programme was therefore developed which provided for independent appraisal of 5–20% of the localities by higher-level health officials and special teams. Where it was found that less than 85% of villages or urban sectors in an area had been searched, the entire search process was repeated in that area. As time passed, the minimum standard was raised to 90% and the areas chosen for assessment were deliberately selected to include those least likely to have been well covered, such as the villages furthest from health units and those with a high proportion of migrants or very poor populations. Similar approaches were adopted for assessment in the other countries.

The initial assessments were comparatively simple to make, being based on the statement of the village leader or the villagers themselves that a search worker had been in the area and the finding of a smallpox poster or marking on a wall (Plate 10.35). More sophisticated assessment became possible when house-to-house searches began and a reward was offered. Individual households were then asked whether they had been visited by a search worker, whether they knew the amount of the reward and whether they knew where to report cases of smallpox. Later, when workers endeavoured to detect cases of measles, chickenpox and other

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Plate 10.35. In some villages and towns, as here in Barisal, Bangladesh, search workers made a special mark on the wall of every fifth or tenth house. This was evidence for the assessment teams that the area had been visited.

illnesses with rash, the incidence of these diseases in different areas was compared and those in which few such cases were reported were searched again by special teams.

Assessment itself involved large numbers of people. In India, for example, 3 million households in 107 000 villages were routinely visited following each search. The numbers were smaller in Somalia, but finding the scattered villages and nomad camps made the task no less challenging.

The value of assessment in the search programme suggested its possible use for other purposes; this was demonstrated in Bangladesh (Joarder et al., 1980), in which teams also evaluated the availability and utilization of tube-wells in rural areas, contraceptive pills (and public awareness of family planning methods), and rural health centres. In other areas, data regarding the occurrence of measles, tetanus, poliomyelitis and blindness were obtained.

Surveillance teams were especially important in the planning and assessment of the search programmes and in other types of search procedure. Until 1973, there had been few of them in Asia, and they had been inadequately supervised and primarily responsible to state or district authorities; from 1973 to 1975, their numbers grew rapidly, proportionately more being assigned to areas in which smallpox was endemic. Those responsible for surveillance over the largest

areas were directed by a national or international epidemiologist, each with a vehicle, and accompanied by a health inspector, 1–2 vaccinators and a driver. At intermediate levels, the teams were headed by young physicians or health inspectors, also with a vehicle, and in some heavily infected local areas 3–4 vaccinators with bicycles or motor cycles constituted a team. The best of the supervisory staff and vaccinators were selected for the teams and trained over a period of 1–2 weeks, followed by supervised field experience under a programme epidemiologist. In Ethiopia, in which health personnel were few, the programme relied from its inception entirely on 2-man surveillance teams, each with a vehicle; most consisted of an Ethiopian health officer or sanitarian and a foreign volunteer. They enlisted the help of local health staff and others wherever they could be found, including young students who had been sent to work in the countryside. Somalia's surveillance programme, which started in 1977, relied primarily on teams headed by WHO epidemiologists and staffed by local health workers.

In each country, areas and groups were identified in which smallpox incidence had been or was then unusually high, together with groups which posed a threat of spread of the disease as a result of their migratory movements. Special searches by surveillance teams were scheduled, for instance, at construction sites, farms, refugee camps, nomad encampments and the poorer urban areas to which rural immigrants flowed. Border areas, whether between countries or provinces or states, were also found to be poorly served by their health administrations and were often areas of high incidence. Nomads could usually be intercepted at river crossings or mountain passes and sometimes also when they assembled to assist in the harvest. In Afghanistan and Somalia, special cards were issued to leaders of nomadic groups, certifying that the groups had been seen and vaccinated by a surveillance team, and indicating where and when they had been

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QAADO 200 SH

JAMHUURIYADDA DIMOQRAADIGA EE SOOMAALIYA
MASHRUUCA CIRIBMIRKA FURUQA
DIIWAANKA BAAFISKA FURUQA

MAGACA MADAXA
Name of Headman

TAARIIKH DATE	MEESHA LABAAREY WHERE SEARCHED		MAGACA BAAFIYAHA NAME OF SEARCHER
	MEESHA LOCALITY	DEGMO DISTRICT	

WAA IN LAGA HELAA AQALKA MADAXA

Plate 10.36. Leaders of nomadic groups in Somalia were issued with special cards on which search workers recorded when and where they had contacted the group.

Plate 10.37. The ceremonial presentation of a reward for discovering a case of smallpox in Kuralia, Bangladesh. The formality of a public occasion lent dignity to such events and attracted attention to the rewards.

contacted. The cards were subsequently useful in assessing the efficacy of search among nomads.

Special search programmes were required for areas especially difficult of access. Each country had a number of such areas, usually with a small, widely dispersed population and few health services, where teams often had to travel by boat, horse or camel or to walk for one or more weeks. Where variola major had been present, as in Asia, it was possible through facial pockmark surveys to determine the recent past history of smallpox. Such surveys in Bangladesh, India, Pakistan and Nepal during 1975–1976 revealed only a few small outbreaks which had occurred earlier but not been reported (Ježek & Kanth, 1978; Nair, 1978; Basu et al., 1979; Ježek et al., 1978b; Joarder et al., 1980). This was partly because of infrequent contact between the inhabitants of these isolated areas and those of the more populated endemic areas and partly because of the traditional practice of isolating patients that was followed by many tribal peoples.

The remote areas of Ethiopia and Somalia presented a different challenge. Variola minor had been present in these areas during recent decades, rarely leaving persistent facial pockmarks. Because the disease was mild, patients were usually not isolated and smallpox persisted for long periods. Repeated searches were required to confirm the absence of smallpox, and these were conducted in many areas of both Ethiopia and Somalia as well as in the southern Sudan (WHO/SE/74.67, Bassett et al.; Foster et al., 1978; Ježek et al., 1981; Tekeste et al., 1984).

Ultimately, the most effective method of ensuring prompt reporting proved to be to offer a reward. This had first been done in Indonesia in 1972, when a large outbreak was discovered in what was thought to be a smallpox-free area of Java (see Chapter 13). Numerous illnesses with rash were reported but none proved to be smallpox. Later that year the practice was adopted in Karnataka State in India, and soon thereafter in several southern states of that country, all of which were free or virtually free of smallpox. The rewards ranged from 10 to 25 rupees (US$1.30 3.25). The practice of offering a reward was slow to be adopted more widely, however, because many national and state

Table 10.11. India and Somalia: sources of reports of outbreaks

Source of report	India, 1974–1975		Somalia, 1977	
	Number of outbreaks	% of total	Number of outbreaks	% of total
House-to-house searches	1 946	62	52	37
Field investigations	928	29	9	6
Reports by members of the public	249	8	67	48
Other[a]	38	1	13	9
Total	3 161	100	141	100

[a] Includes market searches and other special searches by teams.

officials feared that it would establish a precedent whereby a reward would be expected for the report of any illness. This fear proved to be unfounded.

At the beginning of 1974, most Indian states sanctioned a reward of 50 rupees (US$6.25), rising to 100 rupees (US$12.50) at the end of 1974 and to 1000 rupees (US$125) in July 1975, shortly after the occurrence of the last case. The offer of even larger sums was considered but programme staff believed that too large a reward would cease to be credible. Even the amounts mentioned represented scarcely believable sums in a country in which workers were sometimes paid 10 rupees or less per day. Initially, the rewards were not well publicized by the health workers, who wished to keep them themselves; but the problem was resolved by offering 2 rewards, one for the person who reported the case and the other for the health worker who investigated it. Only 2 countries besides India offered a reward while cases were still known to be occurring: Bangladesh in mid-1974 and Somalia in April 1977. In Bangladesh, 220 000 takas (US$27 280) were paid in all, a modest sum for the improvement in reporting which occurred. The total expenditure in rewards is not known for India or Somalia, but it is believed to have been substantially less than in Bangladesh.

Rewards were also offered in other countries after they became free of smallpox but, although many suspected cases were reported, none was confirmed. Finally, in 1978, the World Health Organization offered a reward of US$1000 for the reporting of a case that could be confirmed; this, too, brought to light a great many suspected cases with rash due to many different causes. Although none proved to be smallpox, the offer of the reward was of value in confirming that eradication had been achieved.

Many approaches were used to publicize the reward but studies showed that the most effective was simply for search workers and surveillance teams to talk to the people. In surveys in both urban and rural areas of India, 70–85% reported that they had learned about the reward from a search worker; even higher figures were recorded in Somalia.

In 1975, when smallpox incidence had decreased to very low levels, other techniques were used in case detection. Health centres and hospitals were asked to enter the names and addresses of all suspected cases in a "rumour register" so as to obtain a record of such cases which could later be checked by surveillance teams; specimens were taken in increasing numbers from patients with chickenpox in order to ensure that errors in diagnosis were not being made; and surveys were conducted over wide areas to detect persons with facial pockmarks in order to determine whether any had had smallpox after transmission had apparently been interrupted. These activities continued throughout the certification period and were among the important steps taken to certify that transmission had been interrupted (see Chapter 24).

Of the many methods used to detect cases after 1973, in India house-to-house search was clearly of the greatest importance, followed by field investigations of the cases detected (Table 10.11). In Somalia, however, reports from the public in response to the offer of the reward previously mentioned were more important, that offer having begun to be publicized in April 1977 before house-to-house searches had been organized. Because of the reward, young nomads found it profitable to search widely for cases and many reports were received from them.

Containment measures after September 1973

In the change of strategy which began in the autumn of 1973, the initial concern was to ensure the prompter and more complete

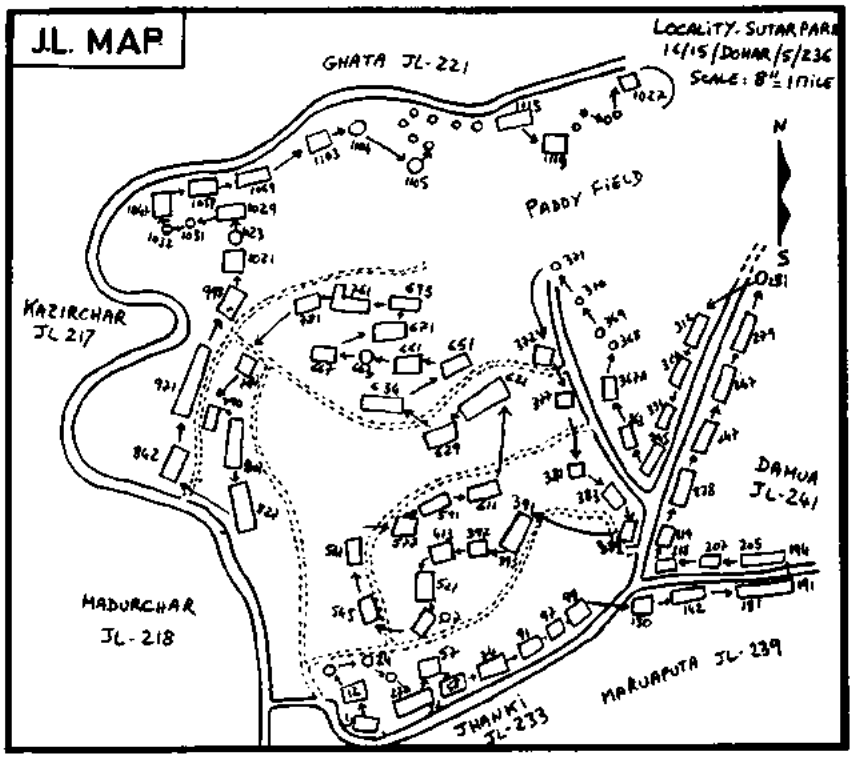


Plate 10.38. A sketch map of an infected village, prepared for containment activities in Bangladesh. All the houses were numbered; arrows indicated the order in which the houses were to be searched.

detection of cases. It was expected that the outbreaks could then be effectively contained by smallpox eradication staff in the conventional manner. The discovery of more than 10 000 cases in India during the first search in 1973 was unexpected and, in many areas, the numbers of outbreaks proved to be far beyond the capacity of existing staff to deal with. In heavily infected areas, help was at first sought from existing health staff but this often proved counterproductive, since those who discovered cases soon found themselves burdened with the additional task of containing the outbreaks. Accordingly, arrangements were made to ensure that those who searched were not also responsible for containment.

Because of the difficulties in developing search operations and the large numbers of cases, containment in all countries until the summer of 1974 continued to consist in little more than the isolation of the patient, a rapid survey to detect additional cases, and the vaccination of household contacts and those in some 30 surrounding households. It gradually became apparent that these measures were inadequate, since outbreaks which were thought to have been contained not only persisted but also spread to other areas. That summer, as numbers of smallpox cases decreased substantially, it became possible in India to assess carefully the failures in containment and to develop special measures to correct them. Over the succeeding months, containment measures became increasingly stringent, making it necessary to engage many additional workers, often locally recruited and trained. Other countries subsequently adopted similar measures.

Measures were taken to ensure more complete vaccination coverage in the outbreak area, the first step being to assign responsibility for each outbreak to a team leader who was a member of the smallpox eradication programme staff. He prepared a sketch map of the affected locality (Plate 10.38) and employed a team of local health workers to paint numbers on the doors of the houses or, in the case of tents, on WHO smallpox recognition cards, which were then attached to the entry flap of each tent. All residents of the village or district of a town were listed by name and by house before containment vaccination was begun, since it was found that fewer persons were then successfully hidden in an effort to avoid

vaccination. The vaccination programme, which followed the listing, required 1–3 days, the team leader and a number of vaccinators remaining in the village for 1 or more nights so as to vaccinate those who were absent during the day. Eventually, a vaccinator remained in an infected village for 28 and, later, for 42 days following the onset of the last case in order to vaccinate visitors, ensure that the patient remained isolated and detect promptly any additional patients who had been vaccinated too late in the incubation period to be protected. In Somalia, 1 or 2 vaccinators usually travelled with each affected group of nomads throughout this period.

For areas outside an infected village but within a radius of 8–10 kilometres, other teams moved from house to house to search for cases and to vaccinate. Because of the density of the population in many of the infected areas in Asia, this sometimes meant contacting 10 000 or more persons, a process that often took 1–2 weeks.

Wherever possible, patients were isolated in their houses, but even this required special measures. To ensure isolation, 4 guards were

Plate 10.39. **A:** Programme staff move from house to house to seek out cases and to register all persons resident in an Indian village. **B:** A WHO epidemiologist, L. B. Brilliant, shows the smallpox recognition card in Bihar State, India, and inquires about possible cases in the area. **C:** A surveillance worker records the discovery of an 8-year-old boy with smallpox in Sidamo, Ethiopia.

hired who were instructed that at least one of them must remain at the door of the house, day and night, entry being permitted through a single door, the other doors being nailed shut. They made certain that the patient remained in the house, vaccinated all visitors and brought the necessary food, water and firewood to the patient. Two at a time were expected to be on duty during each 12-hour period so that, if one had to leave, the other would remain. They stayed until the patient's last scabs had separated and were paid for their services at that time. Supervision was simplified by telling them that if, at any time, a supervisor found the house unguarded, all would be discharged without pay and new guards hired. Eventually a special book was provided in which the guards recorded the

Plate 10.40. **A:** A smallpox isolation hut in Baidoa, Somalia. **B:** An isolation camp for smallpox patients in English Bazar, West Bengal State, India.

name of each visitor, the date and the fact that he or she had been vaccinated.

In Ethiopia and Somalia, where many people lived in tents or small huts, and in congested areas of Bangladesh, it was difficult to isolate patients in this manner. In these countries, therefore, 2 other methods were sometimes used. The first was to construct for the patient a small separate hut with kitchen and latrine facilities and to surround it by a barrier of thornbush or bamboo. The second was to isolate the patient in a specially constructed camp occupied only by smallpox patients. Special guards were used in both cases. It was often difficult to gain the agreement of Ethiopian and Somali patients to be isolated, however, because, having the mild variola minor variety, they had few symptoms and could work and move about without difficulty. Compliance increased when all patients, on recovery, were given new clothes, their old clothes then being burnt.

From early 1974 onwards in India and later in Bangladesh and Somalia, larger numbers of national and international epidemiologists were recruited to head surveillance teams, with the aim of providing at least 1 such team for the supervision of surveillance and containment in an area with no more than 25 active outbreaks, an outbreak being defined as the occurrence of 1 or more cases of smallpox in a geographical location, such as a village, district of a town or nomad encampment. When a patient moved from one village to another—to be hospitalized, for example—this was counted as 2 outbreaks, since both areas had to be kept under surveillance. Once an outbreak was identified, it was considered "active" until 28 (later 42) days after the onset of the last case of smallpox. By this time, the patient's last scabs would have separated and any contacts who were incubating infection would have developed disease.

The surveillance teams were responsible for visiting each outbreak at least weekly to ensure that the prescribed measures were being taken; when the appropriate interval had elapsed after the onset of the last case, they were also responsible for organizing a search of the area lasting 1–2 days before certifying that the outbreak could be removed from the master list of active outbreaks.

Outbreak investigation required time and patience in order to identify with accuracy the dates of onset of all cases and the probable sources of infection of each so as to reconstruct its development. For this purpose, and to promote an understanding of the concept of the chain of transmission, a special form had been employed since 1970. As the number of epidemiologists increased and the number of outbreaks decreased, more elaborate forms began to be used.

The surveillance team was responsible for investigating the source of infection or contacts of patients if they were in villages within its area of responsibility, but if the villages concerned were outside its area, the team notified its superiors so that other teams could investigate. However, the transmission of accurate information from one area to another regarding possible sources of infection and patient contacts proved unexpectedly difficult. The names of contacts as well as those of towns and villages often had to be spelled phonetically, since informants were usually illiterate. Whether this information was transmitted by telex, messenger or telephone, there were often difficulties in locating the persons or even the villages named.

The quality of supervision provided by the teams was proportional to the number of outbreaks and, as outbreaks became fewer, ever more intensive measures were applied, with the result that smallpox incidence showed an accelerating decline from June 1974 in India, and from the spring of 1975 in Bangladesh, when a similar approach was used there.

Measurement of progress

As has been noted above, it became the practice in 1973–1974 to record and monitor the number of active outbreaks rather than the numbers of reported cases. This focused the attention of programme staff specifically on surveillance–containment activities and, as a result, several standards for use in measurement were developed, designed to appraise the effectiveness of such activities.

The interval between the onset of an outbreak and its detection reflected the effectiveness of case detection. It was believed that it should be possible to detect at least 75% of all outbreaks within 14 days after the onset of the first case. This proved difficult. In India, a level of 57% was achieved during 1974–1975; in Bangladesh just over 70% in 1975; and in Somalia, 60% were discovered after intensive activi-

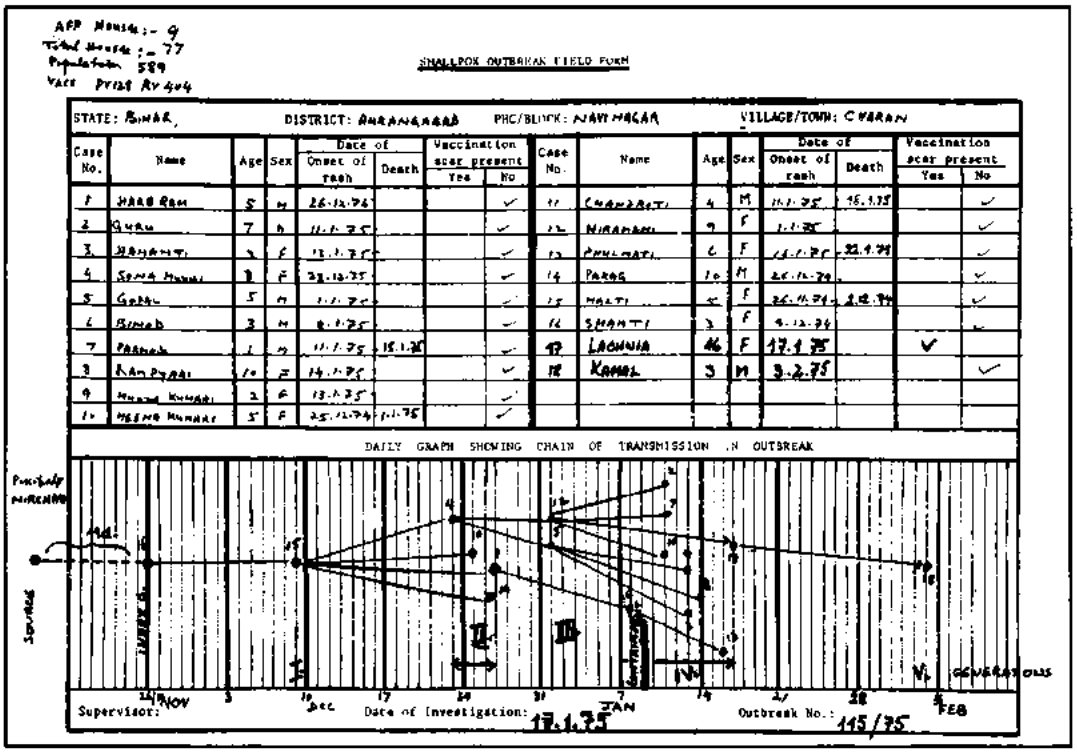

SMALLPOX OUTBREAK FIELD FORM
DAILY GRAPH SHOWING CHAIN OF TRANSMISSION IN OUTBREAK
Supervisor:
Date of Investigation: 17.1.75
Outbreak No.: 115/75

Plate 10.41. Form for outbreak investigation which provided in the upper part for basic data about cases and, in the lower, for plotting them by date of onset to show the spread from patient to patient. The roman numerals indicate the generations of cases. The outbreak plotted here occurred in Bihar State, India, in December 1974 and January 1975.

ties began in April 1977. However, by determining why in each instance the interval was longer than that prescribed, problems in detection were identified and the necessary changes in field operations could be made.

The response of containment teams was measured by the *interval between the discovery of the outbreak and the beginning of containment activities.* Ideally, containment should have begun on the day a case was reported, but this depended on the availability of manpower and transport. In most areas, there was a rapid response. In India, containment was started in 60% of newly discovered outbreaks on the day they were discovered; in less than 10% was it delayed for 3 days. In Somalia, containment was started on the day of discovery in only 40% of outbreaks when the programme began in April 1977 but in more than 90% by August.

The effectiveness of containment measures was assessed by the *interval, in days, between the beginning of containment and the occurrence of the last case.* This indicator was closely followed in all programmes from the autumn of 1974 onwards. The standard laid down was that no case of smallpox should occur in any outbreak more than 20 days after containment had started. This interval was long enough for containment vaccination to be completed and for smallpox to develop among those who had been vaccinated too late in the incubation period to be protected. From early in 1975, all outbreaks in which cases occurred more than 20 days after the start of containment activities were investigated by a senior epidemiologist to determine the reasons for failure and to advise on corrective measures.

The effectiveness of containment varied widely from area to area but improved with time. In India, additional cases occurred after 20 days in 25–30% of outbreaks in 1974, but in only 5% during 1975. In Bangladesh, a more rigorous interval of 15 days was prescribed as the standard. From November 1974, cases occurred in 25% of outbreaks after 15 days, a proportion which gradually decreased to less than 10% by June 1975. In Ethiopia, in 1973, smallpox persisted for more than 20 days in fewer than 25% of

outbreaks and the figure remained at or below this level until transmission ceased.

CONCLUSIONS

Smallpox had many attributes which greatly facilitated its elimination; the strategic plan for eradication was a comparatively simple and inexpensive one; and, in principle, all countries supported the concept of an eradication programme coordinated by WHO. As has been pointed out in this chapter, however, implementation of the smallpox eradication programme was neither simple nor straightforward, and its successful outcome, even as late as 1976–1977, was by no means assured. The execution of this global programme, like that of any other, was inevitably complicated by a host of natural and political problems ranging from floods, drought, famine and war to such human failings as incompetence, dishonesty and personal antagonisms. These alone gave rise to formidable difficulties. No less of a problem was that of obtaining and sustaining a commitment to the programme on the part of national governments and international agencies alike, however beneficial for all peoples the global eradication of smallpox was seen to be. In consequence, serious shortages of resources and lack of cooperation continually hampered progress. Although an understandable scepticism prevailed at first as to the feasibility of eradicating this or any disease, problems persisted even when it was clear that eradication was imminent and continued throughout the process of certification.

Nevertheless, the global eradication of smallpox was ultimately achieved, a success which can be attributed essentially to four factors. The first and most important of these was the existence of an international organization through which a collective international policy could be expressed and which could call on governments and individuals in fostering and coordinating activities directed towards a common purpose. Although the execution of the programme was sometimes less than optimum, no other agency could have obtained the requisite cooperation and international commitment and participation to achieve an objective of this magnitude.

The second important factor was the dedication and competence of a substantial cadre of both national and international staff, many in their 30s and 40s, who continually learned from experience—adapting, innovating and creating to enhance the programme's activities. They, in turn, served to stimulate and to inspire the large number of national health staff whose potential had never been fully realized.

The third factor was that the strategic plan was stated in terms of principles and illustrative methodologies rather than of directives. Moreover, the WHO Handbook explicitly encouraged programme staff to explore alternative approaches and anticipated that changes would be made as experience was acquired. As a consequence, each national programme was different and each evolved and changed over time. In addition, experiences and observations in one area were rapidly communicated to others and then appropriately adapted and applied.

Finally, the fourth factor was the recognition in 1967 that, however much was known about smallpox and however adequate the tools for eradication appeared to be, continuing research both in the field and in the laboratory would be essential. Thus, research was actively promoted throughout the course of the programme and scientists from all parts of the world responded to WHO's requests with extraordinary generosity and commitment, commonly making their observations available long before publication. Without the contributions provided by research, the achievement of smallpox eradication would have been doubtful at best.

The programme itself developed with surprising rapidity from 1967 to 1973, employing few international staff and comparatively straightforward methods of mass vaccination and surveillance–containment. In large measure, this success, where earlier efforts had failed, can be attributed to the use of quality control in the programme, something that had been uncommon in most of the endemic countries. Testing in international laboratories ensured that vaccine was potent and stable; assessment of vaccination campaigns determined whether the proportion of vaccination takes was satisfactory and the coverage adequate; and improved reporting systems provided evidence of progress towards the ultimate objective of the programme—the absence of smallpox cases.

In 1973, when endemic smallpox was confined to 5 countries in the Indian subcontinent and eastern Africa, increasing resources became available through voluntary

contributions, permitting an intensification of work in the problem areas. Surveillance–containment programmes in the 5 countries concerned became steadily more sophisticated and activities began to be documented in greater detail. Increasing numbers of international and national staff were recruited for full-time service and printed forms for recording data increased markedly both in number and in the amount of detail they contained. Without this effort, smallpox transmission would have persisted far longer than it did, if indeed eradication could have been achieved at all, given the population density and movements of peoples in the Indian subcontinent, war in Ethiopia, and the suppression of reports of smallpox in Somalia.

Until 1973, successful national programmes required only a few international advisers in addition to their own health personnel, and a handful of simple forms. Case detection and containment programmes were simple and relied heavily on existing health service units. This is not adquately reflected in the published literature, as most papers deal with programmes during the period 1973–1977 and suggest a pattern of activity which, although necessary then, was not characteristic of programmes in the more than 20 countries which succeeded in eradicating smallpox before 1973.

Chapters 12–22, which deal with national programmes, describe more fully the wide variety of activities carried out, the problems, the successes and the mistakes. What was apparent in all, however, was the potential for extraordinary achievement on the part of WHO and national health service staffs acting in concert, given proper guidance and appropriate support in coordination, management and the allocation of resources. The potential for success in eradicating smallpox was greater in 1967 than anyone initially believed; the potential for successfully applying measures for the control or elimination of other diseases is far greater 20 years later.

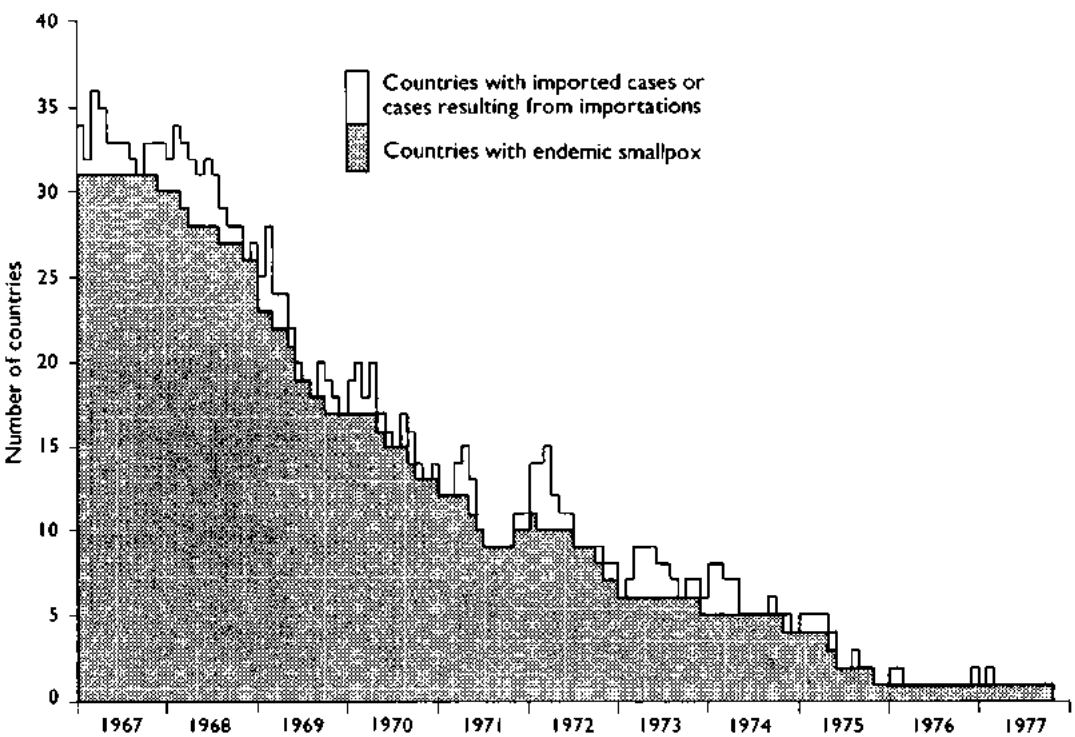


Fig. 10.4. Number of countries with endemic or imported smallpox, by month, 1967–1977.

A CHRONOLOGY OF PROGRESS, 1967–1980

Introduction

This section presents a year-by-year summary of progress in smallpox eradication (Fig. 10.4) to provide a frame of reference for the chapters describing the eradication programmes in individual countries or groups of countries (Chapters 12–23) and the certification of eradication (Chapters 24–27).

In compiling the data on the incidence of smallpox over the years, we have reviewed the available and sometimes conflicting reports and have made use of the figures that in our opinion most accurately reflect the situation at the relevant time. Some figures differ from those previously published and from those in the official national and international records. The differences are greatest for the early years of the programme, when notifications of reported cases were most delayed and incomplete. The reader who wishes to refer to the contemporaneous figures may consult the *Weekly epidemiological record*, which provided a compilation of the most recent information every 2–3 weeks and a summary of the status of the programme as a whole twice a year.

Throughout the course of the Intensified Smallpox Eradication Programme, particular importance was attached to defining which countries had endemic smallpox and which did not. Although this might seem a straightforward task, it was not so, especially during the first few years and for the smaller countries. The first summary of the situation in this period was provided in a report by the Director-General of WHO to the forty-first session of the Executive Board, which met in January 1968. In that report, 29 countries or territories were identified as being "endemic" (30 if East Pakistan, which later became Bangladesh, and West Pakistan are considered separately). Later information led to Cameroon, Southern Rhodesia and Yemen being added to the list; each had reported only a few cases in 1967 and these were at first assumed to represent importations, but they were not. However, 2 small countries—Lesotho and Swaziland—were mistakenly shown as having endemic smallpox in 1967 because of their proximity to infected areas in South Africa and their rudimentary reporting systems. Subsequent information suggests that both were smallpox-free. In later years, other countries were mistakenly identified as non-endemic because of government suppression of smallpox notifications. This occurred for Iran from 1970 to 1972, for Iraq from 1971 to 1972 and for Somalia in 1976. Later information received from government and other sources served to clarify the situation.

The Situation at the Start of the Intensified Programme, 1967

The first year of the Intensified Smallpox Eradication Programme saw a substantial acceleration of activities compared with previous years. This was primarily the consequence of greater financial resources and more staff becoming available from WHO and of the implementation of the regional programme in western and central Africa that received direct support from the USA. Certainly this enhanced effort started none too soon, for the number of reported cases of smallpox in the world rose in 1967 to 131 776, one of the highest totals for a decade. Little of this increase can be attributed to better reporting since few countries had yet improved their case-notification procedures. Indeed, it soon became evident that reporting was even less complete than had been feared; it had been thought that perhaps 1 case in 20 was being notified, but experience in the field began to indicate that a figure of 1 in 100 was probably nearer the mark.

The 31 countries or territories classified as having endemic smallpox (see box) were in 4 epidemiological zones sufficiently separate to make it unlikely that if one was freed from smallpox, it would become reinfected from another. These were: (1) Brazil, (2) Indonesia, (3) Africa south of the Sahara, and (4) a contiguous group of southern Asian countries extending from Afghanistan through West Pakistan, India and Nepal to East Pakistan. The eastern borders of East Pakistan and India were taken as the eastern limit of endemic smallpox on the Asian mainland, although Burma had imported cases from 1967 to 1969. The People's Republic of China was not in relations with WHO in 1967 and provided no official information, but reports by visitors suggested that smallpox was not present there; the government confirmed this in 1973.

Programme implementation

Basic strategies and principles were issued in July in a WHO *Handbook for Smallpox Eradication in Endemic Areas*, and these were endorsed in September by the WHO Scienti-

fic Group on Smallpox Eradication. Surveillance reports giving epidemiological information and documenting progress in the countries were widely distributed by WHO from September on.

WHO gave priority to the eradication programmes in the smaller of the major epidemiological zones—Brazil and Indonesia—in the expectation that success there would free resources that could be concentrated on the larger and probably more difficult zones. Brazil's programme had started in 1966, and Indonesia and WHO agreed in December 1967 on one to start in 1968. Eradication programmes began or were under way in 12 of the other 29 endemic countries at the end of 1967. Programmes in Cameroon, Dahomey, Ghana, Mali, Niger, Nigeria, Togo and Upper Volta were included in the regional western and central Africa programme supported by the USA; a programme in the Democratic Republic of the Congo started late in the year; and WHO-supported programmes were continuing in Afghanistan, Nepal and Zambia, although only the last of these represented a meaningful effort.

Many other countries decided to undertake programmes and developed plans of operations with advice from WHO; the procurement of supplies began as each plan was finalized. In India, however, a serious problem was posed by the government's decision in December 1966 to terminate its 5-year-old vaccination campaign. That country was then reporting more than one-third of the world's cases. Appealed to by WHO, it agreed that a joint India–WHO team should undertake a field assessment of the situation late in 1967 and develop an alternative plan.

Other developments

In May the first annual meeting of WHO regional and Headquarters officers responsible for smallpox eradication was held to discuss and agree upon plans, needs and priorities. In December there was held in Thailand the first of many intercountry meetings at which the staff of programmes in different countries and their WHO counterparts exchanged experiences and debated strategies.

The supply of potent, stable vaccine being crucial to success, arrangements were made for laboratories in Canada and the Netherlands to test vaccines and to help countries to develop their own production. At the same time, WHO initiated a survey of the vaccine quality and production capacity of laboratories throughout the world. More than 200 batches of vaccine were tested under WHO's auspices in 1967 (43 batches in 1966, 12 in 1965). All countries were asked to contribute vaccine and by the end of the year 15 million doses had been distributed by WHO, 4 times as many as in 1966. Over and above this, the USSR provided more than 75 million doses, mainly to Afghanistan, India and Burma, and the USA about 25 million doses for use in Africa.

After trying and rejecting several cheaper variants of the jet injector, which had come into operational use in 1967, WHO assessed the capability of the bifurcated needle—a new device by which a very small amount of vaccine could be introduced almost painlessly into the skin by multiple punctures. By the end of the year it had proved to be the instrument of choice.

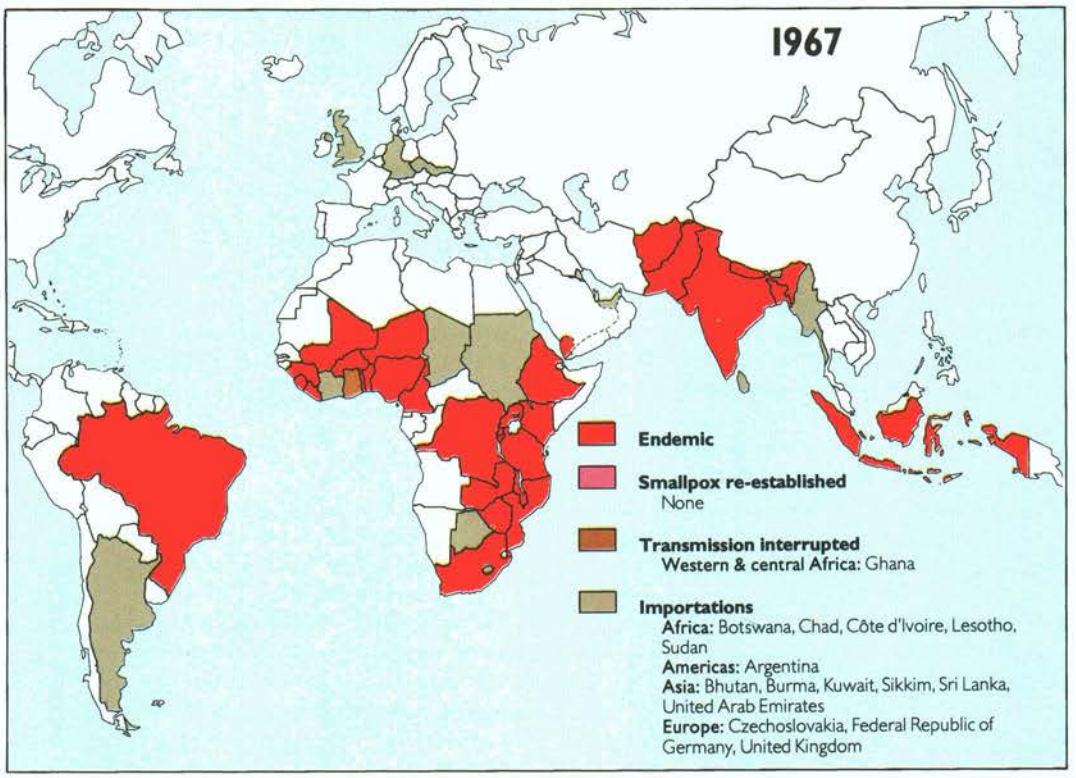
Countries or Territories with Endemic Smallpox in January 1967

Africa, eastern and southern: Burundi, Democratic Republic of the Congo (Zaire from 1971), Ethiopia, Kenya, Malawi, Mozambique, Rwanda, South Africa, Southern Rhodesia (Zimbabwe from 1980), Uganda, United Republic of Tanzania, Zambia.

Africa, western and central: Cameroon, Dahomey (Benin from 1975), Ghana, Guinea, Liberia, Mali, Niger, Nigeria, Sierra Leone, Togo, Upper Volta (Burkina Faso from 1984).

Americas: Brazil.

Asia: Afghanistan, East Pakistan (Bangladesh from 1971) India, Indonesia, Nepal, Pakistan (West Pakistan until 1971), Yemen.



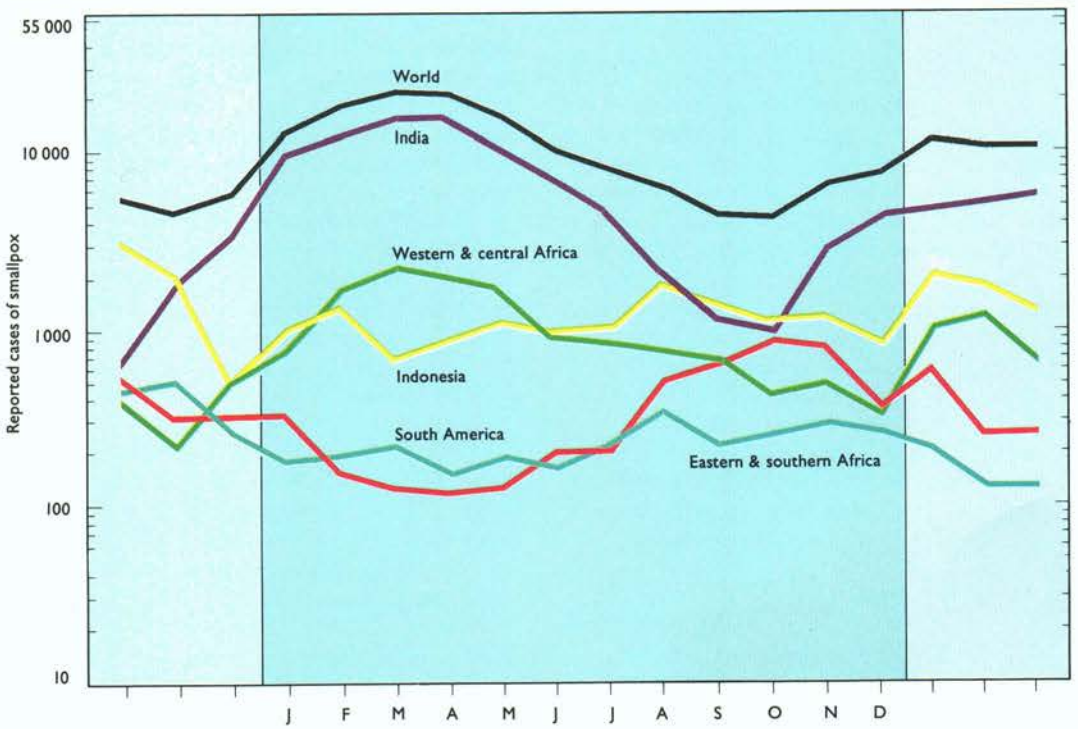


Plate 10.42. Smallpox in the world, 1967: endemicity in 31 countries or territories.

The Situation in 1968

During the second year of the Intensified Programme, the number of endemic countries with special eradication programmes increased from 12 to 19, and agreements were reached or appeared imminent for the commencement of programmes in 8 others. However, 4 remained as problems—Southern Rhodesia, South Africa, Mozambique and Ethiopia. The first two, with which WHO had no official contact, caused little immediate concern as they reported few cases and had a reasonably extensive health infrastructure. However, civil war in Mozambique precluded an extensive programme there, and Ethiopia declined to initiate a programme.

The number of countries with endemic smallpox in 1968 remained at 31, transmission having stopped in Ghana in 1967 but Sudan becoming infected following importations from Ethiopia. The number of reported cases diminished from 131 776 to 79 951 but this was almost entirely accounted for by a decrease in India (from 84 902 to 35 179 cases). Whether this represented better smallpox control in India or simply a longer-term cyclical trend in the incidence was unknown.

Africa

The most heartening progress was made in the regional programme in western and central Africa, which included some of the world's poorest and most heavily infected countries. By the end of 1968, 62 million persons had been vaccinated—almost 60% of the total population; in September special surveillance–containment programmes began in many of the countries. There was a sharp drop in the number of cases reported and 6 of the 10 remaining endemic countries interrupted transmission. However, civil war in Nigeria, the most populous country, threatened to extend throughout the country. In eastern and southern Africa, Uganda and Zambia also stopped transmission.

South America

Brazil, the only endemic country in the Americas, made notable progress in its vaccination campaign and, by the end of the year, was vaccinating 1.3 million persons each month. There was little improvement, however, in the notifications or the surveillance programme. Neighbouring countries in South America also conducted vaccination campaigns but cases—all due to importations from Brazil—were detected only in French Guiana and Uruguay.

Asia

The programme in Indonesia began in 1968 and within 6 months transmission was interrupted throughout East Java, a province with more than 25 million persons. Although special vaccination campaigns were begun or intensified throughout Indonesia and other endemic Asian countries, progress was generally poor and reporting was little improved.

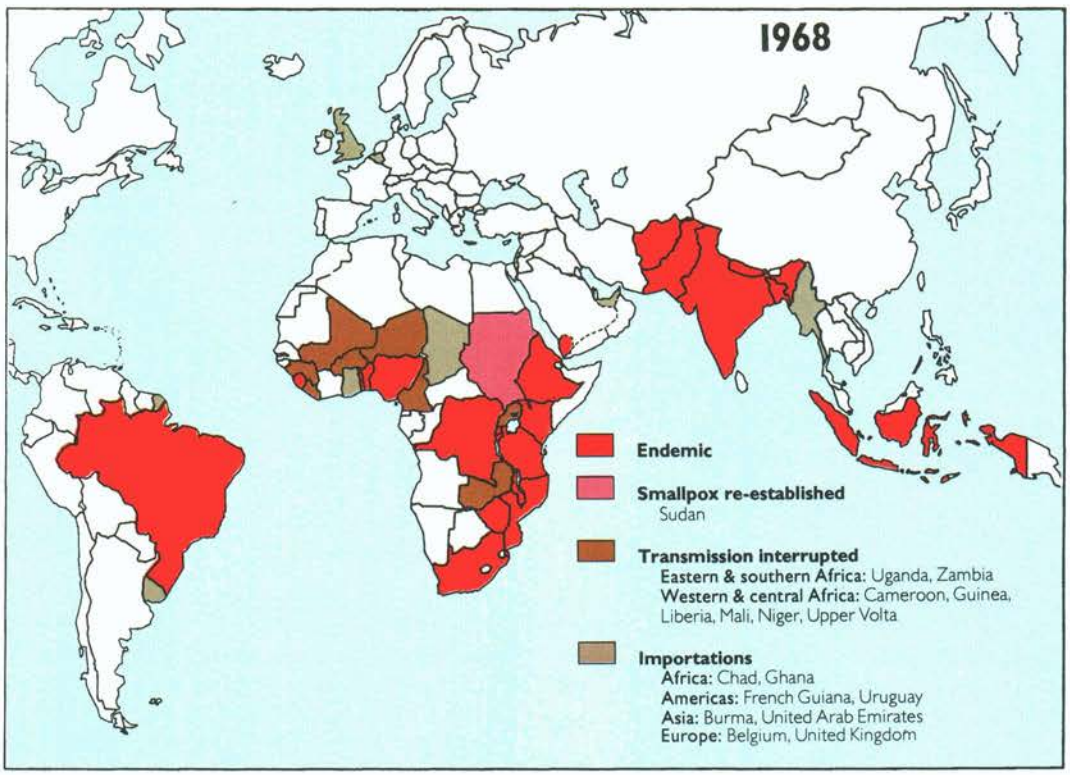
Other developments

The lack of attention to surveillance was a matter of special concern and surveillance was stressed as being "as important as the vaccination programme itself" at the Twenty-first World Health Assembly in May and emphasized again at an intercountry seminar in Kinshasa in November. Special training materials were developed to foster an understanding of the principles and methods involved.

The bifurcated needles, introduced for general use, alleviated some shortages of vaccine, but it became apparent that the endemic countries would soon need to produce much more vaccine. WHO convened experts in vaccine production to develop a manual on production methodology, and the Organization sent consultants to 24 laboratories and provided equipment and reagents to 30.

The dissemination of information about the programme and about field observations was facilitated as reports about the programme began to be published every 2–3 weeks in the *Weekly epidemiological record* from May onwards and other documents were distributed regularly to senior eradication staff throughout the world.

Activities during the first 2 years of the Intensified Programme laid a sound foundation but how this could be built upon in the field was uncertain. Although the progress in western and central Africa was encouraging, the resources made available there by the USA were greater than could then be foreseen for other countries; progress elsewhere was made primarily in the countries with the more advanced health services. At the end of 1968, the feasibility of global smallpox eradication was by no means certain.



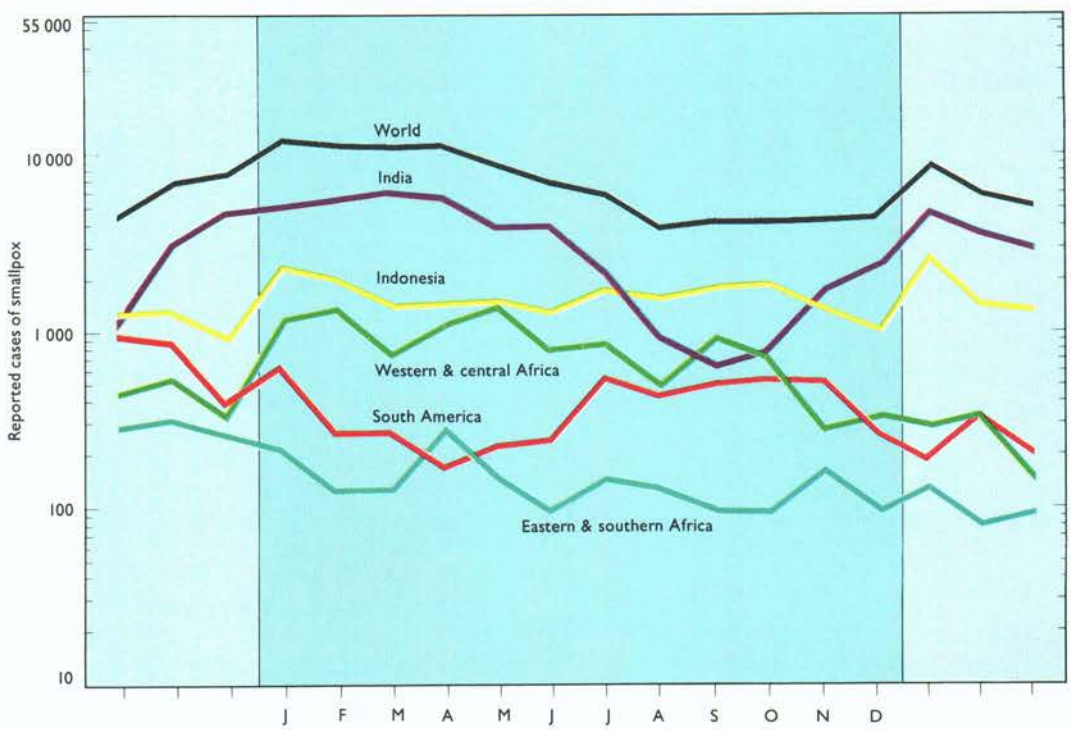


Plate 10.43. Smallpox in the world, 1968.

The Situation in 1969

Certain evidence of progress came during the third year of the Intensified Programme. Only 23 countries recorded endemic cases that year—8 fewer than in 1968—and in 5 of them transmission was interrupted. Thus, during a period of only 3 years, 15 countries successfully eliminated smallpox. Except for Yemen, they were all in Africa, and 10 of them were in western and central Africa where, at the end of 1969, smallpox persisted only in northern Nigeria. Kenya and Mozambique also ceased to report cases but because surveillance was inadequate there, the absence of cases was viewed with scepticism at first.

Although improved notification procedures led to more complete reporting in several countries, the total number of cases reported in the world declined to 54 199, the lowest figure that had ever been recorded. The optimism this gave rise to was tempered, however, by the realization that none of the countries in which transmission had been stopped was large, only Kenya having a population of as many as 10 million persons.

Africa

The successes in Africa were encouraging but 4 of the largest countries still presented serious problems. The programme in the Democratic Republic of the Congo progressed well but the country was one of the largest in Africa, transport presented formidable problems and smallpox was prevalent everywhere. In the Sudan, smallpox spread widely after being imported and civil war throughout its southern provinces made activities impossible there. In November, Ethiopia, which presented the greatest logistic challenge, reluctantly agreed to a programme but it could not begin until 1971. About South Africa, little was then known except that the number of reported smallpox cases increased from 43 in 1967 to 246 in 1969.

South America

Brazil intensified its vaccination campaign and began surveillance programmes in 4 states. Because of this, notifications improved and the number of reported cases increased from 4372 in 1968 to 7407 cases in 1969. Near the end of the year, however, the principal surveillance officers were discharged and the director of the programme resigned.

Asia

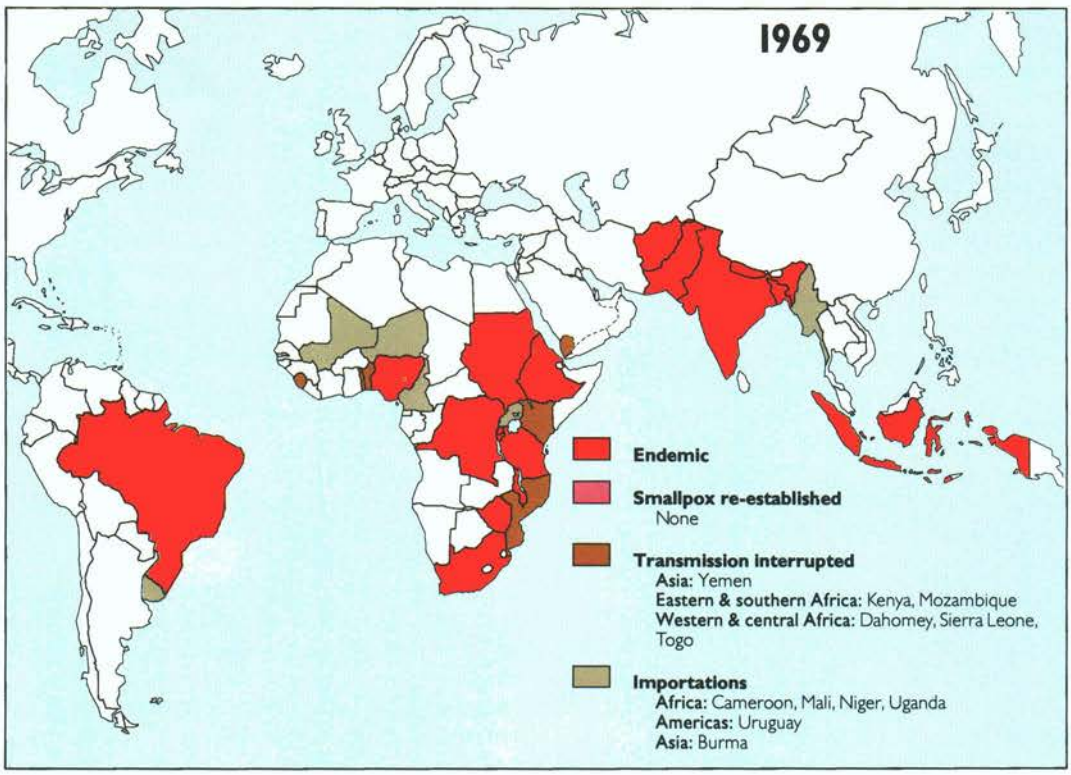
The programmes in Afghanistan, Indonesia and Nepal were substantially strengthened during 1969 but there was little progress to report in either India or Pakistan. Mass vaccination campaigns in East and West Pakistan were far behind schedule and surveillance activities were nominal, at best. India postponed the signing of an agreement to strengthen its programme and, in 1969, reported more births than primary vaccinations. India's decision that year to begin using the bifurcated needle and to terminate the use of liquid vaccine was almost the only encouraging news from a country which each year continued to report one-third to one-half or more of the world's cases of smallpox.

Other developments

Vaccine production increased in a number of the endemic countries in 1969, but shortages could be foreseen as the year progressed and more programmes began. Despite appeals for additional donations of vaccine, the quantities contributed in 1969 were smaller than in 1968.

The attainment of global eradication rested on the premise that there was no animal or other natural reservoir of the virus, but firmer evidence of this was required. In March 1969, the first of a series of biennial meetings of an informal group of research workers was convened by WHO in Moscow to plan and implement a collaborative research programme to discover whether any reservoir of variola virus existed and to elucidate the behaviour of the closely related monkeypox virus.

The promotion of surveillance–containment activities continued to meet with limited success and so the Director-General presented a special report to the WHO Executive Board which recommended for every country the "*immediate investigation of every reported case of smallpox by trained investigators, the tracing of the source of infection and the prompt application of containment measures*". In May, a seminar for the countries of western and central Africa provided important documentation of this approach, and another, held in Pakistan in November, for participants from 11 countries of the Eastern Mediterranean and South-East Asia Regions, stressed its importance. Translation of the methods into practice, however, continued to progress slowly.



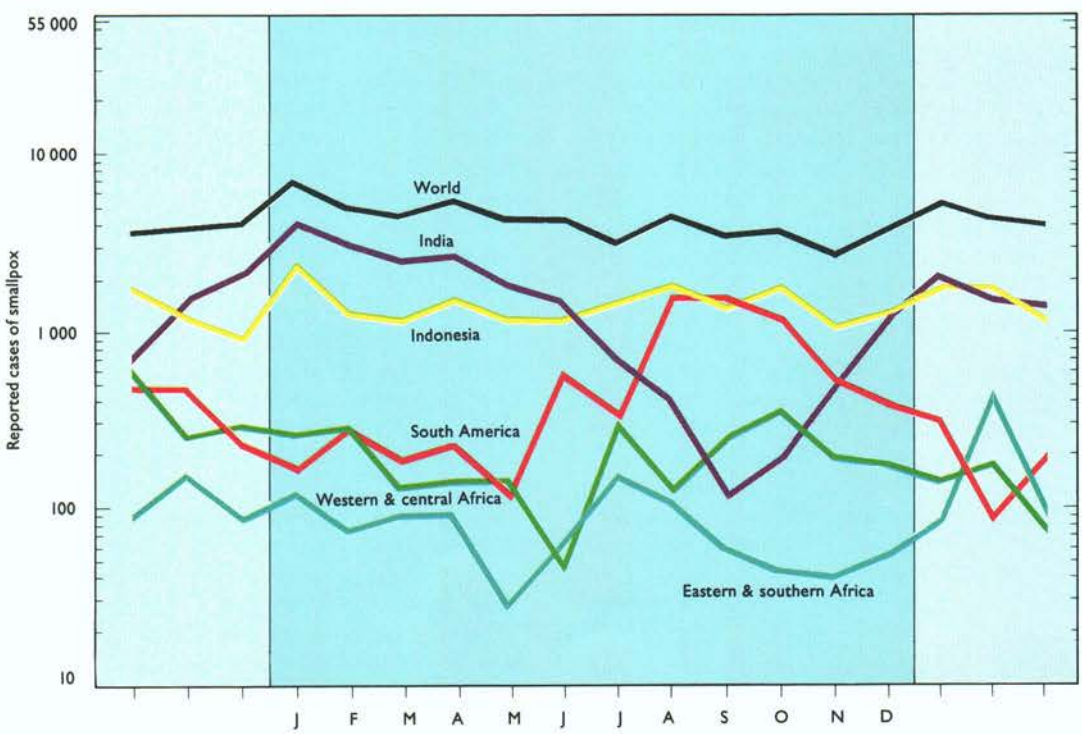


Plate 10.44. Smallpox in the world, 1969.

The Situation in 1970

Developments in 1970 gave grounds for genuine optimism that global smallpox eradication could be achieved: only 18 countries recorded endemic cases during the year and in 6 of these transmission was interrupted—5 in Africa and 1 in Asia. Large populations were involved. With the containment of the last cases in Nigeria in May, more than 100 million persons in western and central Africa were in a smallpox-free region. Wholly unexpected was the elimination of smallpox from the densely populated area of East Pakistan (population in 1970, almost 66 million) following a brief but effective surveillance–containment programme. The reported cases of smallpox in the world during 1970 numbered only 33 693, a decrease of 38% from the record low of the previous year.

Africa

At the end of 1970, smallpox was considered to be endemic in only 5 countries in the whole of Africa: the Democratic Republic of the Congo, Ethiopia, Malawi, South Africa and the Sudan. Excellent progress was made in the Democratic Republic of the Congo during the year and South Africa embarked on a special vaccination campaign. Sudan's programme, however, progressed slowly in the accessible areas and nothing could yet be done in the strife-ridden southern provinces. Ethiopia's programme had not yet started, and the epidemiological situation in Malawi was unclear.

South America

The increased incidence of smallpox reported during 1969 had brought additional resources and support to Brazil's programme; its vaccination campaign accelerated and by the end of 1970 it appeared to be on the verge of interrupting transmission. Programmes in other countries were proceeding adequately and only 1 outbreak was detected, in an Argentinian town on the Brazilian border.

Asia

Indonesia conducted a successful surveillance–containment programme and estimated that by the end of the year 85% of its population resided in smallpox-free areas. Although transmission had been interrupted in East Pakistan and programmes in Afghanistan and Nepal were progressing well, those in India and West Pakistan were not. In West Pakistan, a poorly conducted mass vaccination campaign lagged far behind schedule. India agreed to strengthen its national structure with WHO assistance, but otherwise remained confident as the number of reported cases continued to decrease, only 12 773 cases being reported in 1970 compared with 84 902 cases in 1967. Late in the year, however, it became evident that this was partly an artificial decrease, changes in the national notification system serving to inhibit reporting.

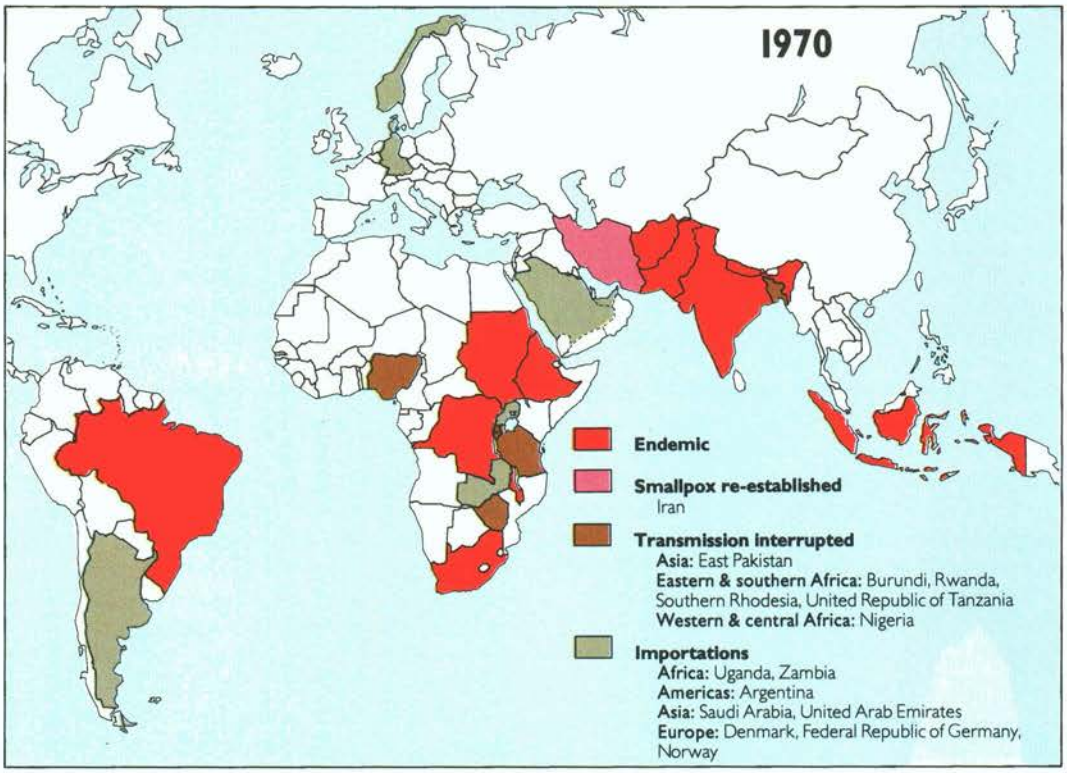
To encourage surveillance–containment activities in Asia, a seminar was held in New Delhi in December 1970 for countries throughout the South-East Asia Region. West African and Indonesian staff described their successes with this strategy but few changes followed.

A significant event, although it was not recognized until a year later, was the reintroduction of endemic smallpox into Iran. Major epidemics were to follow, with spread of the disease to neighbouring countries and eventually to Europe.

Other developments

With more eradication programmes in progress, increasing resources were required. Efforts to obtain additional donations met with little success, and an attempt to have WHO funds that were available in the Americas reallocated for use in Asian countries also failed. Vaccine was short throughout 1970 and donated vaccine frequently had to be dispatched on the very day it was received in Geneva. Towards the end of the year, it became apparent that it would be far more difficult to eradicate smallpox from the remaining endemic countries than it had been in those which had already been freed of the disease.

Another unexpected problem occurred when, in the second half of the year, human cases of monkeypox, clinically indistinguishable from smallpox, were discovered in Liberia, Sierra Leone and Zaire. Although monkeypox was not caused by the variola virus, the question arose whether it might behave like smallpox and be sustained by human-to-human spread. Extensive field and laboratory investigations began immediately but not until the late 1970s could the fears be fully allayed.



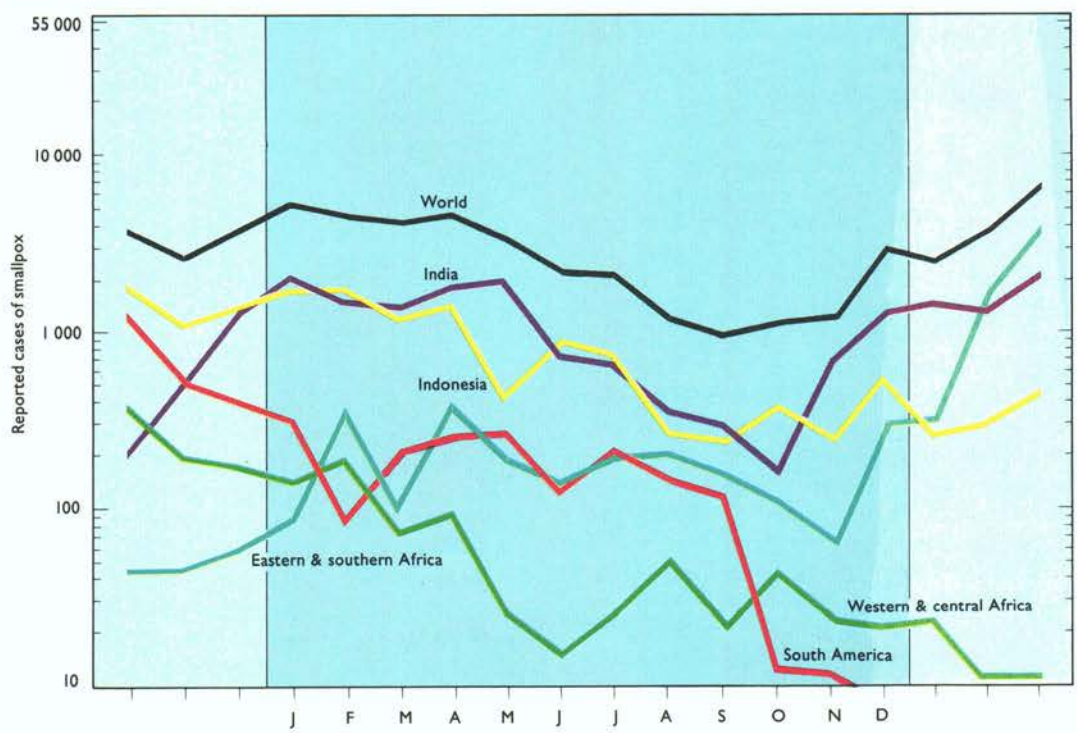


Plate 10.45. Smallpox in the world, 1970.

The Situation in 1971

The fifth and sixth years of the Intensified Programme, 1971 and 1972, were years of transition between the remarkably successful period 1967–1970—when smallpox was successfully eliminated from large areas of the world with few resources—and the succeeding years, 1973–1977, when ever larger resources and more heroic measures were required to stop transmission in the few remaining endemic countries. In some parts of the world remarkable progress was made during 1971, but in others there were setbacks and portents of future problems. The year 1971 began with endemic smallpox in 12 countries, 4 of which interrupted transmission during the year, but 2 others became reinfected—Botswana and Iraq. For the first year since the programme began, the number of reported cases increased, from 33 693 in 1970 to 52 807 in 1971.

Americas

In April, the last cases in Brazil, and in the Western Hemisphere, were detected. Thus, the first of the 4 major epidemiological zones became smallpox-free. A plan of work was immediately developed for investigations and reports that would permit the certification of eradication after 2 years.

Africa

After transmission had been interrupted during the year in Malawi, South Africa and Zaire (formerly the Democratic Republic of the Congo), smallpox was endemic in only 3 African countries at the end of 1971—Ethiopia, the Sudan and Botswana (where it spread widely after having been reintroduced just as the last cases were occurring in South Africa). The programme that started in Ethiopia in 1971 found smallpox to be a far greater problem than had been expected. A staff of fewer than 80 persons detected 26 329 cases, compared with the 722 cases reported in 1970. In the Sudan, smallpox continued unabated in the southern provinces affected by civil war. It was apparent that eradication throughout Africa would need a greatly intensified effort, accompanied by a measure of good fortune, to surmount the problems of civil war.

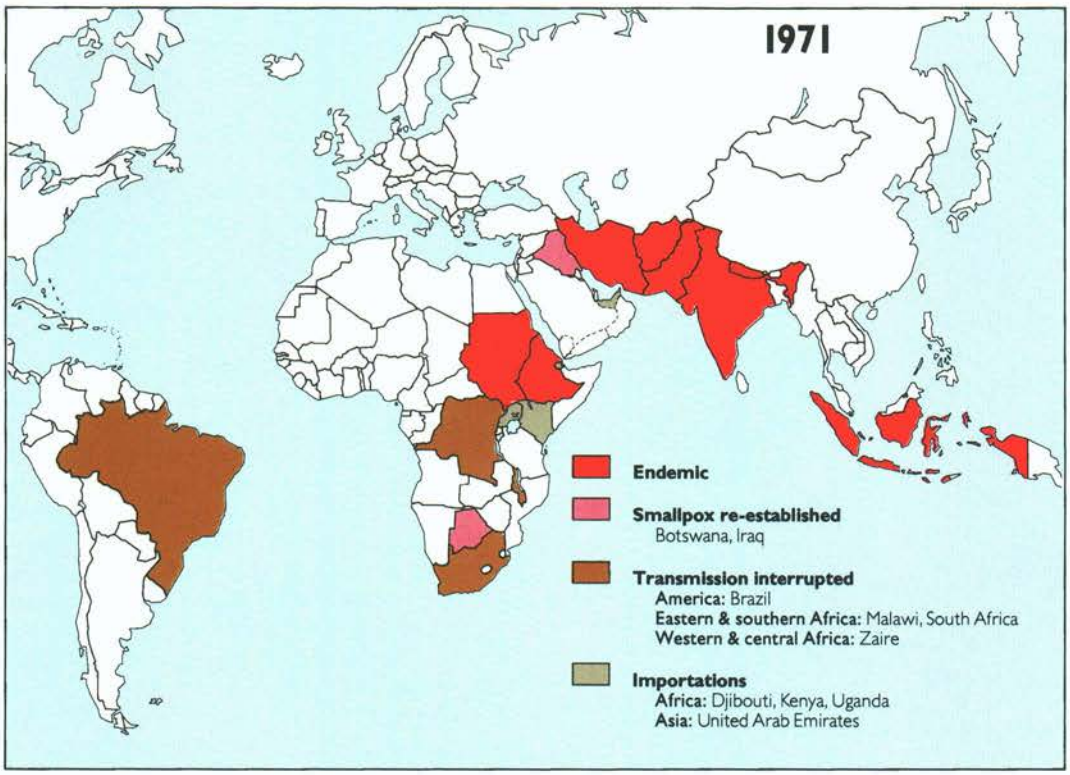
Asia

In Asia, too, both successes and setbacks occurred. The programmes in Afghanistan, Indonesia and Nepal progressed so satisfactorily that, by the end of the year, each appeared to be on the verge of eliminating smallpox. One western state of India (Gujarat), which had been reporting 10% of the world's cases, mounted a highly effective surveillance–containment programme and succeeded in stopping transmission within a year. Epidemic smallpox, however, erupted in adjacent Indian states and, there, satisfactory programmes were slow to begin. During 1971, civil war in smallpox-free East Pakistan (which became Bangladesh in December) caused some 10 million refugees to flee to India, where most of them were housed in special camps in areas in which smallpox was prevalent. Although all persons were supposed to be vaccinated on arrival, this precaution was not taken in several camps, including one of the largest. There, smallpox broke out at the end of the year and spread throughout the camp. In West Pakistan, an unsatisfactory programme was further compromised when the country was divided into 4 largely autonomous provinces and separate programmes had to be re-established in each.

It was in the course of 1971 that the presence of smallpox in Iran first became known through numerous unofficial reports, and the government eventually acknowledged that 29 cases had occurred, all of which were said to have been importations. Much later, it was learned that smallpox had in fact been introduced from Afghanistan in October 1970 and that hundreds of cases had occurred in 1971. Subsequently, it was discovered that the disease had also spread to Iraq in November 1971.

Other developments

Sufficient progress had been made in eradication to cause the authorities in both the United Kingdom and the USA to cease their programmes of routine vaccination in 1971. However, a WHO Expert Committee on Smallpox Eradication, convened in November, presciently observed that "an effort at least equal to that made in the past 5 years" would be required to interrupt transmission in the remaining endemic areas. Although few countries were now involved, they posed difficult problems. To encourage national governments and their smallpox personnel, the WHO Headquarters staff began to spend an increasing amount of time in the field, but additional resources were not forthcoming and vaccine remained in critically short supply.



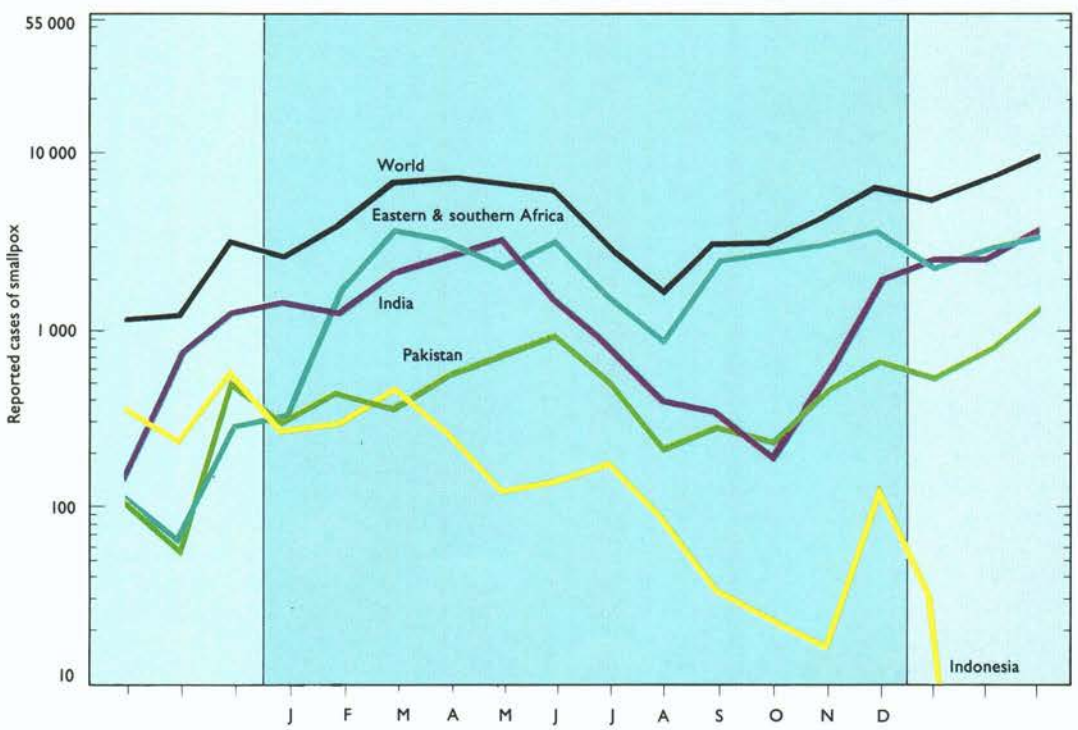


Plate 10.46. Smallpox in the world, 1971: eradication from Brazil.

The Situation in 1972

Like the preceding year, 1972 was marked by notable successes and unexpected setbacks. Overall, the progress was encouraging. There were 10 endemic countries as the year began, but transmission was stopped in 5 of them in the course of the year. Successes in 3 of these—Afghanistan, Indonesia and the Sudan—represented exceptional achievements. The other 2 were Iran and Iraq, for which the true situation was not known with certainty until a year later. The number of cases of smallpox recorded in the world as a whole increased for the second successive year—65 140 cases in 1972 compared with 52 807 cases in 1971—but reporting was more complete and, by the summer, surveillance programmes of some sort were in place for the first time in all countries.

During the first quarter of the year, however, 3 serious problems emerged. In February, epidemics of smallpox began to spread across the newly independent country of Bangladesh as refugees returning from camps in India brought the infection with them. In March, Iraq and the Syrian Arab Republic officially acknowledged the presence of smallpox and soon thereafter a major outbreak occurred in Yugoslavia, imported from Iraq. Finally, in April, a WHO epidemiologist, on arrival in Botswana, confirmed that smallpox had already spread widely there.

Despite these problems, the geographical extent of the infected areas continued to diminish and it was proposed that "the final phase" should begin in September, the objective being a nil incidence by June 1974. Intercountry seminars were held in Ethiopia (September), India (November) and Pakistan (November) to launch this special effort, referred to for the first time as "Target Zero" in an issue of the WHO magazine *World health* and in the first of a series of fortnightly reports circulated by the WHO Smallpox Eradication unit.

Africa

The progress in 1972 in the 3 endemic African countries exceeded expectations. In the Sudan, the civil war in the southern provinces ceased and an effective surveillance–containment programme succeeded in interrupting transmission in December, more than a year earlier than WHO staff had expected. Botswana rapidly mobilized its resources and by the end of the year the interruption of transmission seemed imminent. As Ethiopia's programme gained momentum, the number of reported cases decreased by 35%, from 26 329 in 1971 to 16 999.

Asia

The second of the world's major epidemiological zones became free of smallpox in January, when transmission ceased in Indonesia. This was achieved in less than 4 years and with only a modest amount of international assistance. Afghanistan, where formidable geographical and cultural problems were compounded by the practice of variolation, had once been thought the country in which attempts to eradicate smallpox were the least likely to succeed. Yet it recorded its last endemic cases in October. These successes provided some much-needed encouragement to the other endemic countries of Asia, whose situation was very different. Emergency assistance had been promptly provided to Bangladesh to stem the epidemic of imported cases but, in the post-war chaos, the health services were unable to cope. More than 10 000 cases were recorded, but it is estimated from later studies that more than 100 000 cases occurred. During the autumn, major epidemics began along the densely populated Indo-Gangetic plain in southern Pakistan, India and central and western Bangladesh. Because of the very large numbers of health staff in the Asian countries and the greater interest in eradication taken by the national authorities, hope remained high that the problems might yet be surmounted, but far more serious difficulties were to develop.

Other developments

An epidemic in Yugoslavia, the first in that country for 41 years and one of the largest in Europe since the Second World War, reminded donor countries of the severity of the disease and emphasized the importance of global smallpox eradication. Increased donations of vaccine were received and the debate at the Twenty-fifth World Health Assembly was the most extensive ever, praise for the achievements being mingled with expressions of concern about setbacks in Bangladesh, Botswana and western Asia. Despite the sentiments expressed, however, voluntary financial contributions remained at much the same level as before and WHO even decreased its regular budget allocation for the programme for the following year.

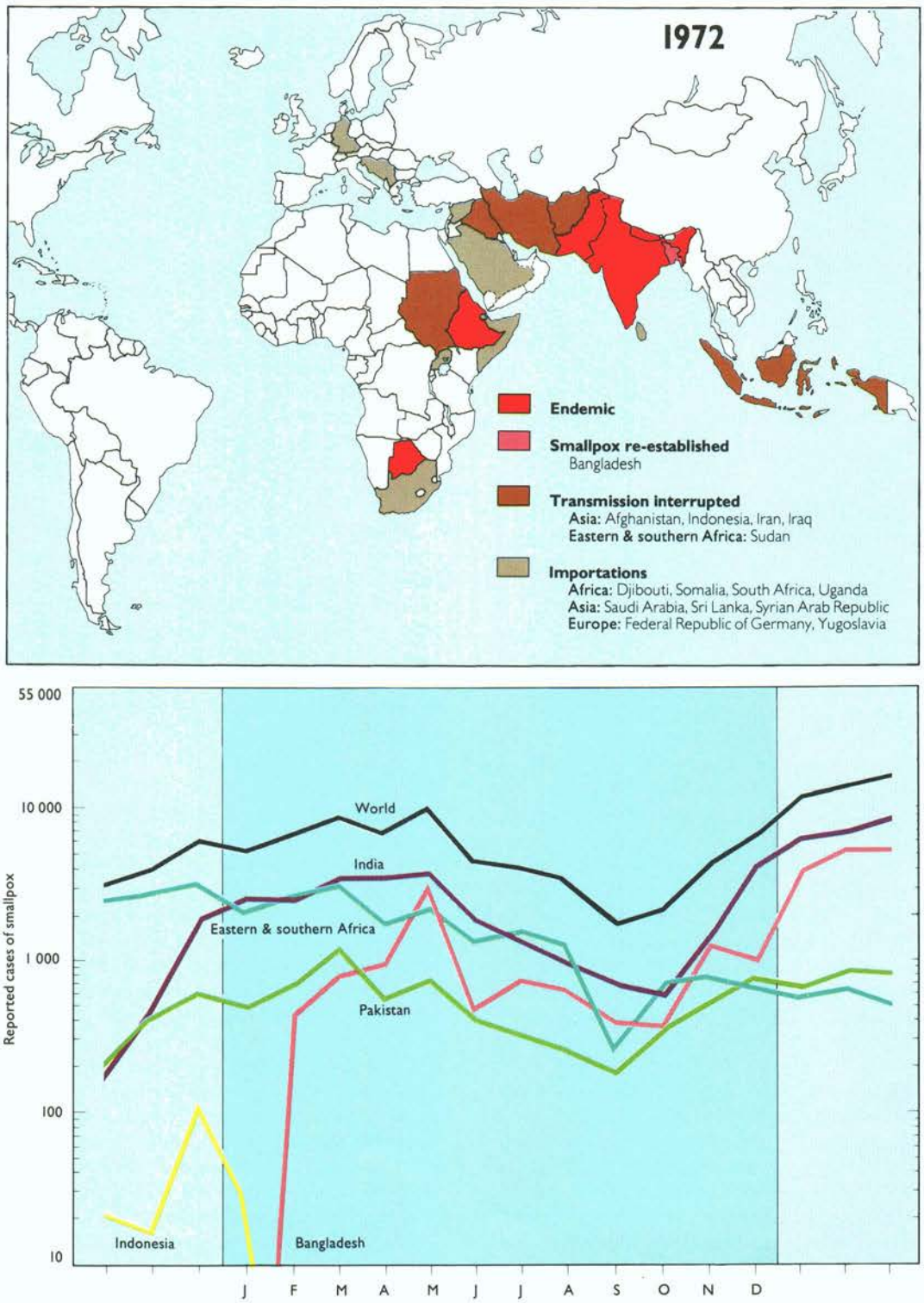


Plate 10.47. Smallpox in the world, 1972: eradication from Indonesia.

The Situation in 1973

The year 1973 marked the beginning of a greatly intensified effort, which steadily increased in tempo from the autumn. As the year began, only 6 endemic countries remained. Among these, Botswana recorded only 27 cases before successfully stopping transmission in November and Nepal reported 277 cases, almost all of which could be shown to have occurred following importations from India. Although the other 4 countries (Bangladesh, Ethiopia, India and Pakistan) reported large numbers of cases, large areas within each of them were free of smallpox or nearly so. It was calculated that 90% of all cases in 1973 occurred over only 10% of the land area of the 4 countries.

Asia

During the first 6 months of the year, the number of cases reported in Asia rose sharply. Although some of this increase was thought to represent more complete notification of cases, surveillance was still by no means fully satisfactory anywhere and epidemics were being discovered of a size not seen since the beginning of the Intensified Programme. By the end of June, almost 83 000 cases had been reported, including some 49 000 in India, 27 000 in Bangladesh and 6000 in Pakistan—totals which were all higher than during the comparable period in 1972.

For these countries, it appeared that a different strategy would be required to eliminate smallpox. The comparatively simple measures for case detection and containment which had previously been effective in Africa were proving inadequate in Asia. The solution proposed was to detect cases more promptly so that they could be contained before further spread occurred. In July, therefore, Indian and WHO staff decided to mobilize all health staff in India to undertake 1-week, village-by-village searches in October, November and December in the 4 states which were then reporting 93% of all cases. In other Indian states 1 or 2 searches would be conducted during this 3-month period. A similar effort was decided upon in Pakistan. The hope was to eliminate most smallpox foci during the autumn, when smallpox spread slowly, and thus to prevent widespread dissemination during the period of rapid transmission from January to April. If this was successful, it was believed that smallpox could be eliminated during the summer of 1974. In Bangladesh, many additional surveillance teams were provided to search for smallpox in schools and markets.

The results were encouraging in Bangladesh and Pakistan, each country reporting an incidence similar to that of the year before despite much more intensive surveillance. In India, however, more than 30 000 cases were discovered between October and December, almost 5 times as many as had been found during the same period in 1972 and, indeed, more cases than had been reported in the whole country during any of the 4 preceding years. The numbers were scarcely believable but the eradication programme staff continued to be optimistic because of the commitment of government officials, the extent of activity and the interest of the health staffs.

Africa

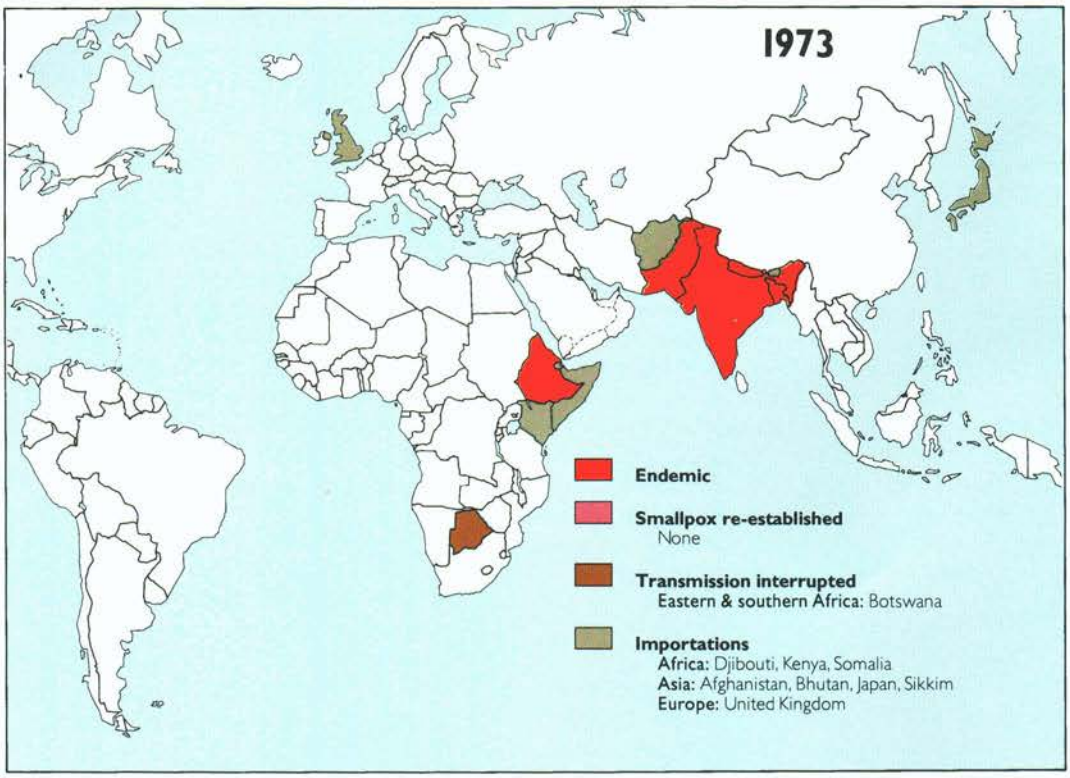
Ethiopia remained the only endemic country in Africa and there, as in Asia, more intensive measures were taken through the addition of staff and the provision of helicopters to help cope with the rugged terrain. The number of reported cases continued to decline despite more complete notifications but logistic difficulties were increasingly exacerbated by mounting civil unrest.

Other developments

During 1973, the first of the international commissions for the certification of eradication examined the programmes in the Americas and confirmed that smallpox had been eradicated from the Western Hemisphere.

A new concern emerged, however, about a possible natural reservoir of smallpox. This arose from the isolation—from monkey kidney tissue cell cultures in the Netherlands and from animal specimens collected near monkeypox cases in Zaire—of what were termed "whitepox" viruses, which were indistinguishable from smallpox virus. The WHO informal research group held its third biennial meeting in 1973 and developed a new agenda of work, but not for several years was this concern finally laid to rest and the "whitepox" viruses shown to be inadvertent laboratory contaminants.

During 1973, the number of recorded cases in the world—135 904—was the highest for 15 years, but the ultimate goal, "Target Zero", appeared none the less to be just over the horizon.



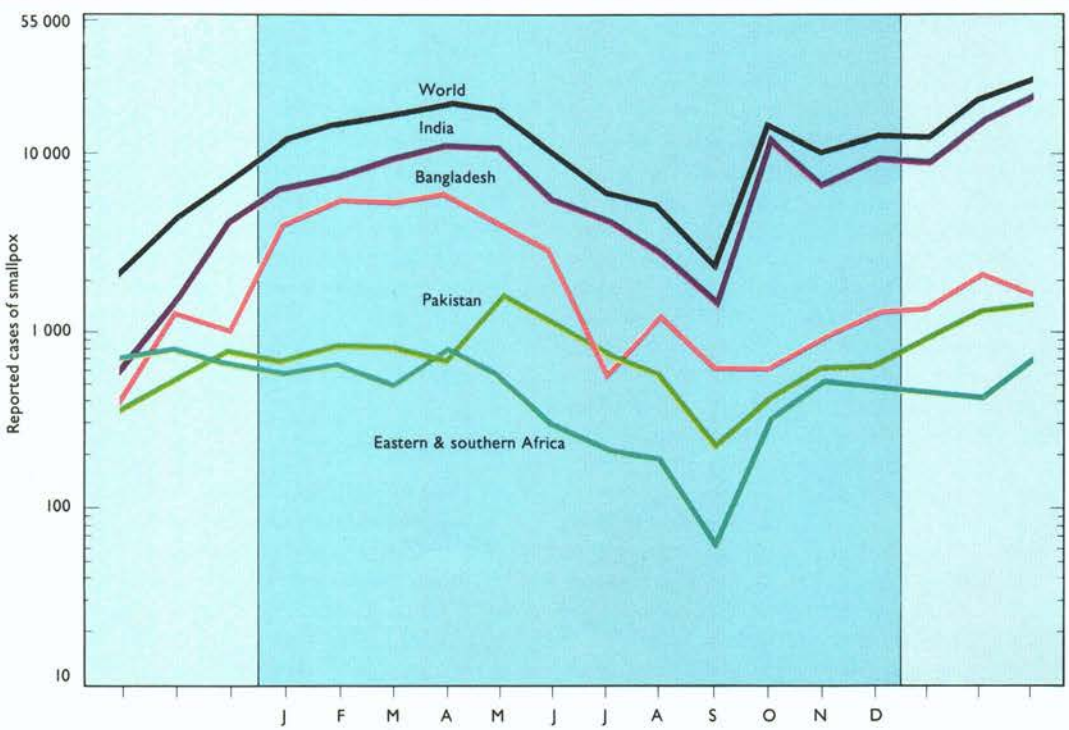


Plate 10.48. Smallpox in the world, 1973.

The Situation in 1974

Throughout 1974, the programme as a whole steadily grew in intensity and accelerated in tempo. Successes in the 1973 autumn campaigns had encouraged the belief that a concerted effort of no more than 6–12 months would see the realization of global smallpox eradication. Additional national and international personnel as well as increased quantities of supplies and equipment supported this effort. It was concentrated on the shrinking endemic areas which in aggregate were smaller than the land area of Pakistan, one of the 5 countries concerned. With eradication apparently imminent, programme staff worked feverishly, driven partly by the fear that unanticipated natural or man-made catastrophes might thwart the achievement just short of the goal. Indeed, this concern proved well founded in 4 of the 5 countries.

Asia

In India, during the first 3 months of the year, intensified search programmes resulted in much more complete reporting but no more cases than in 1973. In May, however, explosive epidemics began, nearly 50 000 cases being detected that month and the worst affected state (Bihar) reporting more than 8000 cases in a week. Work was severely hampered by petrol shortages as well as by strikes which immobilized rail and air transport. Bihar State was further affected by devastating floods in the north, severe drought in the south, and civil disorder. These difficulties were compounded by a major epidemic in an urban industrial centre which resulted in the spread of smallpox to hundreds of distant villages in India and Nepal.

In Pakistan and Bangladesh, other problems occurred. Surveillance in Pakistan's largest province (Punjab) was suspended prematurely by over-optimistic provincial health authorities and an undetected epidemic in its capital, Lahore, quickly spread throughout the province. Bangladesh decided to restructure the health care system, resulting in the suspension of most activities, including those for smallpox, for many weeks. In the summer, monsoon rains brought the worst floods for many years to northern Bangladesh, displacing tens of thousands of persons.

During the first 6 months of 1974, more cases were recorded in Asia than had been reported annually throughout the world for more than 15 years. By June, however, greatly expanded and better organized programmes were functioning and progress began to be measured in terms of the numbers of existing outbreaks (villages or town areas in which 1 case or more had occurred in the preceding 4 weeks). Asia had 8086 outbreaks in June.

Throughout the hot summer monsoon period, all staff were urged to maintain the pace of their work in order to take the fullest advantage of the seasonal decline in incidence. The effort proved successful. Pakistan detected its last case in November, and by the end of the year there were only 517 known outbreaks in all of Asia.

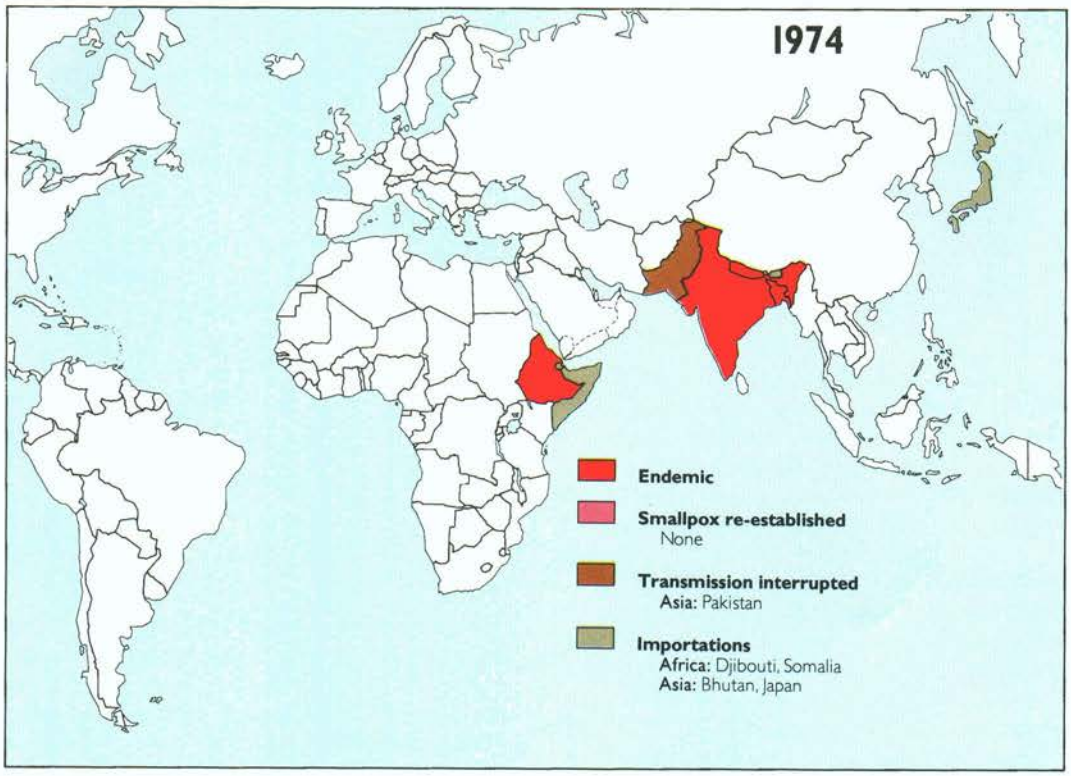
There was optimism that transmission would be interrupted by the summer of 1975. The only doubtful areas were those in which refugees were crowded in Bangladesh. The number of outbreaks in that country, which had been only 78 at the end of October, had tripled by the end of December. More than half, however, consisted of only 1 or 2 cases and hope persisted that, with the planned addition of health staff and temporary workers, the problem could be managed.

Africa

As more support became available, the programme in Ethiopia made steady progress in many areas of the country. The number of reported cases decreased from 5414 in 1973 to 4439 despite more complete notifications; in December, only 166 cases were discovered. In increasingly large areas of the country, however, field operations were severely hampered by the revolution that led to the deposition of the Emperor, by hostilities with Somalia in the Ogaden desert, and by the insurrection in Eritrea.

Other developments

The eradication of smallpox from Indonesia was certified by an international commission in April, but certification elsewhere was deferred pending further progress in Africa and Asia. Increasing efforts were made to recruit suitable international staff and consultants for the intensified campaign and to obtain sufficient contributions of vaccine and funds to permit the work to be sustained. At the end of the year WHO, for the first time, convened a meeting of potential donors to request contributions of US$3.3 million, but only US$2.1 million were pledged.



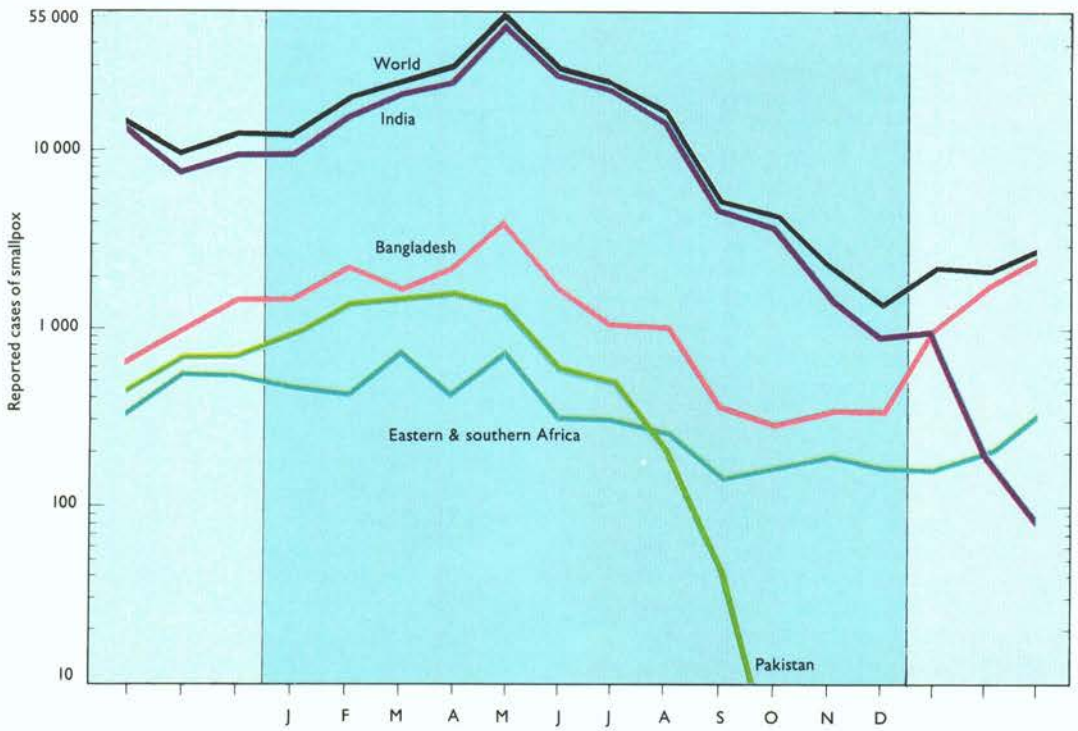


Plate 10.49. Smallpox in the world, 1974.

The Situation in 1975

In 1975, the eradication of smallpox from Asia was achieved and, with it, the end of transmission of variola major virus, which caused the most severe form of smallpox. By the end of the year, endemic smallpox persisted only in Ethiopia, which had 66 known outbreaks, all of which were of variola minor, the mild form of smallpox.

Asia

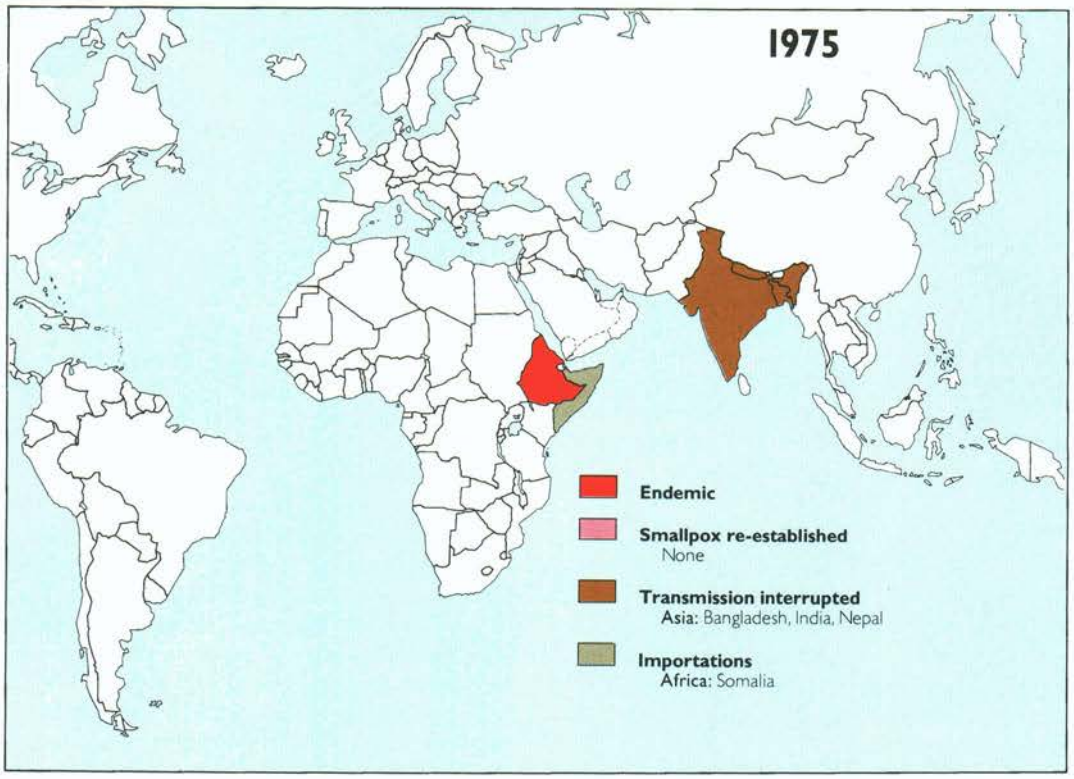
In India and Nepal, the incidence of smallpox and the number of outbreaks decreased steadily. Nepal detected its last case in April and India in May. Bangladesh, however, was the site of yet another catastrophe as smallpox spread rapidly among the hundreds of thousands of persons displaced by floods and famine and from them to settled populations. Despite heroic efforts, the number of outbreaks increased from 78 in October 1974 to 1280 in mid-May 1975. India strengthened activities in border areas and quickly contained the 32 importations that occurred. Emergency funds made available by Sweden and several other countries permitted the recruitment of additional international staff for Bangladesh, and national mobilization by the Bangladeshi authorities resulted in 12 000 persons being fully engaged in eradication work. From May to August, the incidence in Bangladesh diminished rapidly but work had to be partially suspended in August, when the President of the country was assassinated. Officials feared civil war and yet another mass exodus of refugees. Fortunately, the country remained calm, smallpox eradication activities could be resumed, and on 16 October 1975 the last case occurred.

Africa

In Ethiopia, it had been expected that the eradication of smallpox would follow the same pattern as in other African countries, with transmission being interrupted 2–3 years after the programme began. By 1975, however, the Ethiopian programme had been in operation for 4 years and although the staff were few in number, they were capable and strongly motivated. Surveillance–containment activities had been conducted since the start of the programme and more than 10 million persons had been vaccinated—nearly half of Ethiopia's estimated population. Although the population density was low and the habitations widely scattered, the mild variola minor continued to spread. The principal problem area was the rugged highland plateau, where resistance to vaccination was great and where large areas were periodically inaccessible owing to civil war. As a result of the eradication of smallpox from Asia, additional resources could be provided, permitting a 5-fold increase in staff, but the hostilities within the country hampered their efforts.

Other developments

Rumours of cases of suspected smallpox began to be received with considerable frequency from countries considered to be free of the disease. Even though they proved false, arrangements had to be made to investigate each rumour thoroughly and to publicize the findings in order to maintain confidence in eradication. Another emerging problem was that of designing and implementing an appropriate strategy to permit eradication to be certified in the African countries, some of which had detected no smallpox for many years and had consequently stopped their smallpox eradication activities. Certification of eradication in Africa had been deferred until the continent as a whole had become smallpox-free. In 1975, however, it was decided that because of the continent's vast size, the large number of countries, and the diminishing level of smallpox eradication activities, preparations for certification should commence as soon as possible. In February, the first of a number of planning meetings was held, this one being concerned with methods for certification in western and central Africa. This implied that eradication in Africa would be achieved, if not within the year, at least soon thereafter. At the end of 1975, however, that was by no means certain.



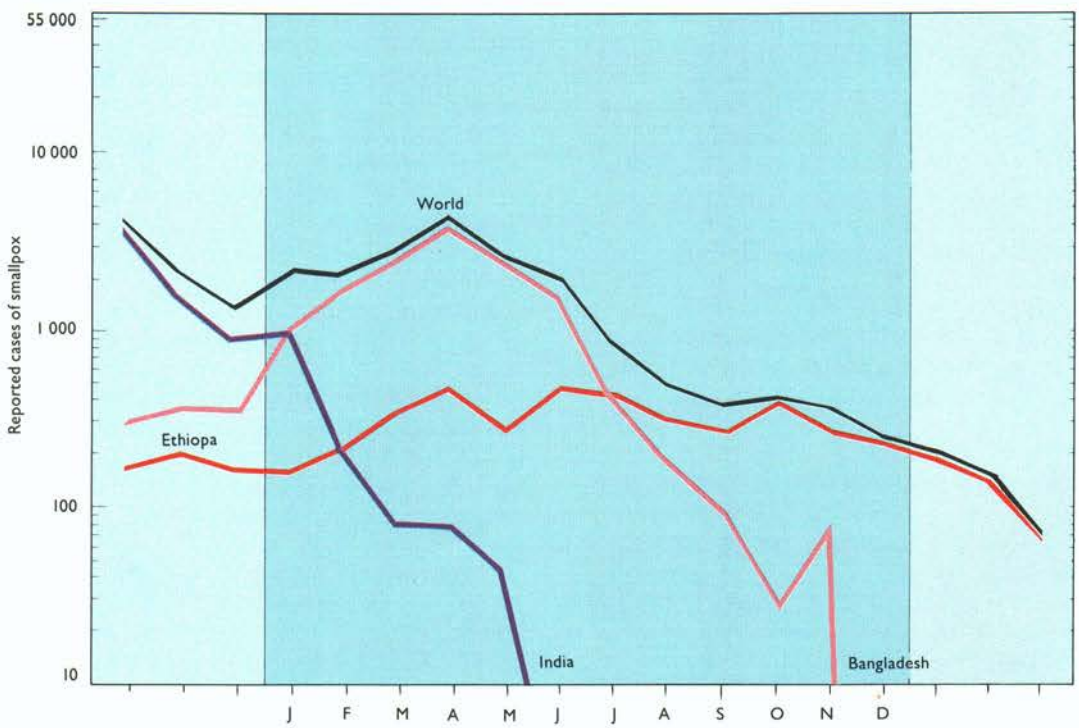


Plate 10.50. Smallpox in the world, 1975: eradication from continental Asia.

The Achievement of Global Eradication, 1976–1977

As 1976 began, smallpox was known to exist in only 66 villages in Ethiopia but the interruption of transmission there and in Somalia, where it became re-established later that year, proved to be as difficult as it had been in mainland Asian countries in 1974–1975. Not until October 1977 was smallpox finally eradicated. A broad range of problems hampered the effort, from difficulties of topography and transport, civil war and eventually war between Ethiopia and Somalia, socio-cultural problems posed by nomads, variolators and large groups who resisted vaccination, to the suppression of reports of cases by the authorities in Somalia.

Ethiopia

Through mid-1976, the resources in Ethiopia were concentrated in the central and northern highland plateau areas in which civil war was raging and most outbreaks were occurring. At great personal risk to the staff concerned, these were gradually contained. Smaller numbers of staff worked in the sparsely settled south-eastern desert, where the few outbreaks occurred primarily among nomads. From past experience in similar areas of western Africa, it had been assumed, erroneously, that smallpox transmission could not long persist in such a scattered, mobile population. In the Ethiopian Ogaden desert, however, variola minor proved to be remarkably tenacious, and operations were frequently interrupted by warfare, the kidnapping of teams and the destruction of vehicles and helicopters. In August 1976, however, the last known outbreak in Ethiopia was contained and, for 7 weeks, no cases were reported from anywhere in the world.

Somalia

From 1972 until February 1976, Somalia had regularly reported importations from Ethiopia, but each was said to have been promptly detected. Late in September 1976, Somalia again reported several imported cases, this time in Mogadishu, the capital. It was learnt later, however, that these were but a few of many cases which were known to the authorities. WHO staff and consultants were quickly sent to help but they were not permitted to visit patients' houses or to travel outside the capital. Repeated mass vaccination campaigns throughout the city failed to stop the spread of smallpox and fully 6 months elapsed before an effective national programme could be established. By then, the disease had spread widely throughout southern Somalia. A large-scale emergency effort was mounted that started in March 1977 and involved adjacent areas of Djibouti, Ethiopia and Kenya. More than 3000 cases were documented before the last case occurred on 26 October 1977.

Other developments

During 1976–1977, certification activities were organized in Asian and African countries, often requiring special studies lasting a year or more before a WHO international commission could be invited to assess the programme and to certify eradication. In April 1976 eradication was certified in 14 countries of western and central Africa, and in December in Afghanistan and Pakistan; in April 1977 in Bhutan, India and Nepal, in June in 9 countries of central Africa, and in December in Bangladesh and Burma.

It became apparent in 1977 that an independent body would be needed to advise on the measures that should be taken to give health authorities throughout the world sufficient confidence in global eradication to be willing to cease vaccination. A group of international experts, which was convened by WHO in October 1977, recommended a number of measures, including the designation by the Director-General of a Global Commission for the Certification of Smallpox Eradication. The Commission was to provide continuing guidance and oversight to the certification process and to report to the Director-General when it was satisfied that global eradication had been achieved.

The question of what should be done about the stocks of variola virus retained in laboratories around the world had long been a troublesome one. The destruction of most, if not all, such stocks was desirable but this required the full cooperation of national governments and of the laboratories concerned. As a first step, a register of the laboratories that held variola virus was prepared. Then, in 1977, the World Health Assembly requested that all variola virus stocks should be destroyed, excepting those held by WHO collaborating centres with maximum containment facilities. Many laboratories soon complied and events in 1978 served to speed the process.

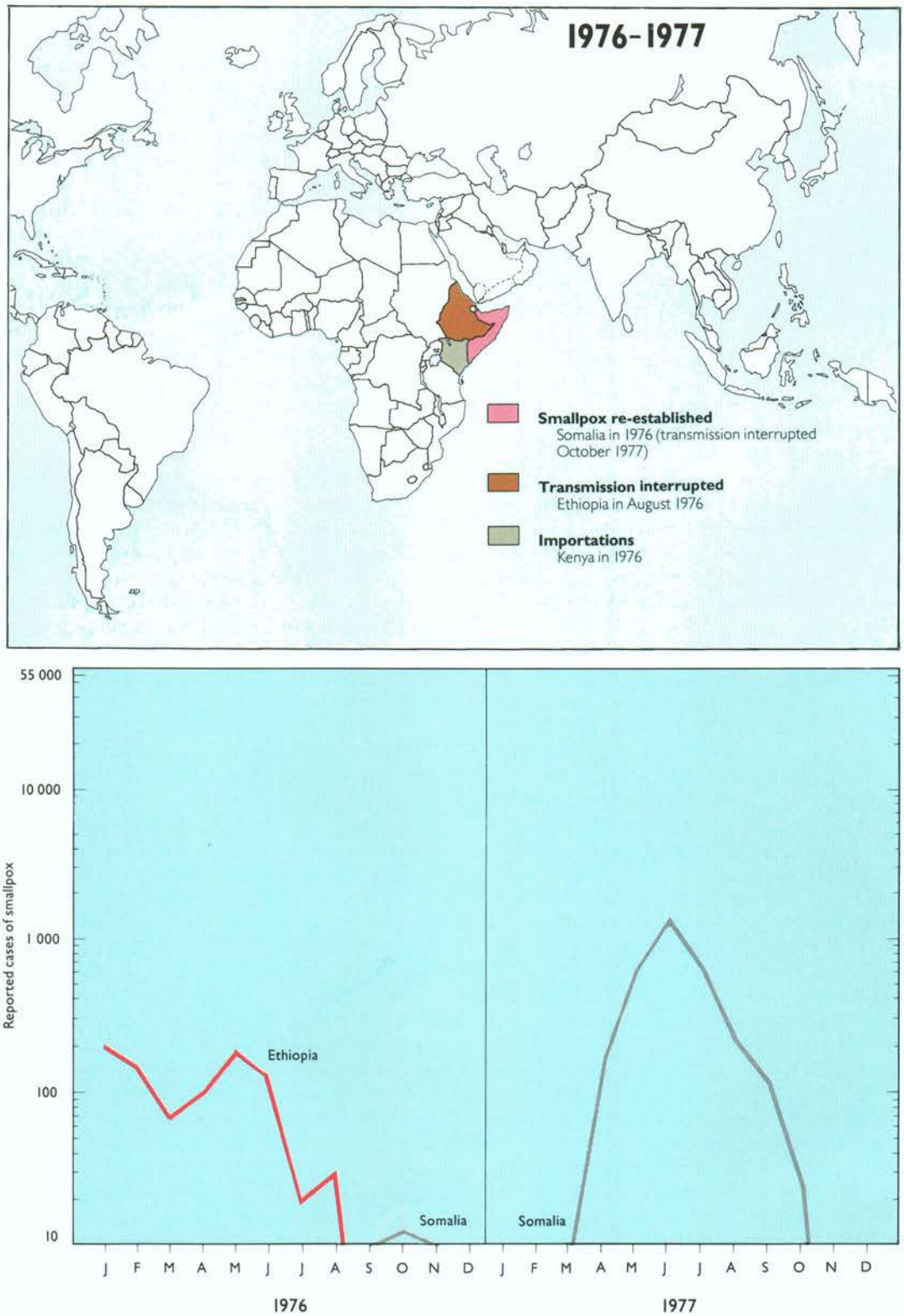


Plate 10.51. Smallpox in the world, 1976-1977: global eradication.

The Certification and Formal Declaration of Global Eradication, 1978–1980

The period between the containment of the last known outbreak and agreement by the Thirty-third World Health Assembly (1980) that global eradication had been achieved was as important but as difficult as had been the preceding years. The world community had to be confident of the attainment of eradication and had to know of the measures which had been taken to certify this. Laboratories had to be persuaded of the need to destroy their stocks of variola virus or to transfer them to WHO collaborating centres. Rumours of possible cases of smallpox had to be investigated and the findings publicized. Research was required to determine the nature of the viruses resembling variola virus which appeared to have been recovered from animals. An assessment of the risk of monkeypox to those living in the tropical rain forests was required as well as a determination of whether that virus could persist by human-to-human spread. Provision also had to be made for the long-term storage of vaccine reserves and for the preservation of records.

However important and substantial the activities which remained, the disappearance of smallpox quickly resulted in a diminished interest in the programme. Only with difficulty were national governments persuaded of the need to assign resources for certification activities, and WHO's budget for smallpox decreased sharply. Remarkably, however, a rigorously scheduled array of activities was completed almost as planned.

During 1978, certification activities were completed in 19 countries, including most of those in southern Africa and western Asia. This brought to 64 the total of countries where eradication had been certified by international commissions. In December, the Global Commission decided that special activities were needed in 15 additional countries. It also recommended that an official attestation be sought from all other countries to the effect that the country concerned had been free of smallpox for at least 2 years. Difficult diplomatic relationships, national sensitivities, civil disturbances and inertia caused serious problems in implementing the recommendations, but one by one the problems were overcome. On 9 December 1979, the Global Commission concluded that the global eradication of smallpox had been achieved and approved a report that was presented to the Thirty-third World Health Assembly in May 1980.

The urgency for laboratories to destroy or transfer their stocks of variola virus became apparent when, in August 1978, 2 cases of smallpox with 1 death occurred as a result of a laboratory infection in Birmingham, England. National authorities took a greater interest in ensuring the safety of their own populations and the number of laboratories retaining stocks of variola virus decreased to 6 by May 1980, and eventually to 2.

In 1978, WHO announced a reward of US$1000 for the report of any new case which could be confirmed as smallpox, and some 50 rumours a year were evaluated in 1978 and 1979 by field investigation and laboratory study. Most proved to be chickenpox; none was a case of smallpox.

Collaborative research on monkeypox and the "whitepox" viruses, conducted in laboratories in Japan, the United Kingdom, the USA and the USSR, revealed the troublesome "whitepox" viruses to have been laboratory contaminants. Field and laboratory studies of monkeypox virus provided increasing evidence that human infections were infrequent and that human-to-human transmission seldom occurred.

Reserves of smallpox vaccine were established and a protocol was developed for the periodic testing of samples to ensure their continuing potency.

Throughout this period, a special public information effort was undertaken to make widely known what had been accomplished and how, so that when the World Health Assembly agreed that eradication had been achieved, the general public would accept the fact more readily.

The declaration on 8 May 1980 by the Thirty-third World Health Assembly that smallpox eradication had been achieved concluded an historic chapter in medicine. Twenty-two years had elapsed since the USSR had first proposed to the Health Assembly that global smallpox eradication should be undertaken, and 14 years since the Assembly had committed special funds to a programme which it hoped would interrupt transmission within 10 years. In fact, 10 years, 9 months and 26 days elapsed from the beginning of the Intensified Smallpox Eradication Programme until the last case in Somalia.

CHAPTER 11

SMALLPOX VACCINE AND VACCINATION IN THE INTENSIFIED SMALLPOX ERADICATION PROGRAMME

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INTRODUCTION

Vaccination against smallpox had been practised in virtually every country of the world, and in many on a large scale, when the Intensified Smallpox Eradication Programme was launched in 1967. By its use, smallpox had already been eliminated as an endemic disease from all but 31 countries, which constituted the hard core of the smallpox problem. It was clear that, in order to implement the programme, one of the first tasks of the WHO Smallpox Eradication unit would be to ensure that enough vaccine was available, of sufficiently high titre and sufficiently heat-stable, to ensure that potent vaccine could be delivered to those needing vaccination in any place in the world, however remote and however adverse the environmental conditions.

Traditionally, smallpox vaccine had been distributed in liquid form, although laboratories in France and the Netherlands East Indies (now Indonesia) had produced air-dried or freeze-dried vaccines from the 1920s onwards. Unless refrigerated, liquid vaccine did not retain its potency for more than a few days whereas, until it was reconstituted, freeze-dried vaccine remained highly potent for over a month at ambient temperatures, even under tropical conditions. During the period after the Second World War, freeze-dried vaccine prepared in France was being used in francophone Africa and by the mid-1950s producers in several countries had developed freeze-dried vaccine production on a commercial scale. From 1959 onwards somewhat larger quantities of freeze-dried vaccine began to be used for smallpox vaccination in tropical countries, but its extensive use throughout the world dates from 1967–1968. After 1971 it was the only kind of vaccine used in any country engaged in a national smallpox eradication programme.

In May 1980 the Thirty-third World Health Assembly, after it had declared that smallpox had been eradicated throughout the world, recommended that smallpox vaccination should be discontinued, except for investigators at special risk. By 1985, smallpox vaccine production had been stopped in most countries and in no country in the world is smallpox vaccination routinely conducted in the civilian population. Vaccine reserves are being kept for emergencies by WHO and by the health authorities of some 20 countries (see Chapter 28). Thus smallpox vaccination has gone full circle. Introduced by Jenner in 1798, it came to be used all over the world until, with the eradication of the disease that it was designed to control, its use has now been abandoned, except for military personnel in some countries. Jenner's prediction, in the paper reproduced in Chapter 6, that "... the annihilation of the Small Pox, the most dreadful scourge of the human species, must be the result of this practice" has been fulfilled, making smallpox vaccination redundant.

An interesting sequel to this history of the rise and fall of smallpox vaccination is that vaccinia virus is currently showing considerable promise as a vector for genes specifying protective antigens against a variety of other infectious agents (see box). If the results of current research fulfil expectations, "smallpox" vaccine may make a comeback as a vehicle for providing simultaneous active immunization against a number of selected viral or protozoal diseases. It has the advantages of heat stability and ease of administration, but the risk of complications will need to be carefully weighed and perhaps a more attenuated strain sought (Quinnan, 1985).

In this chapter, various aspects of vaccine production and vaccination will be described in terms of practices that came into operation after the Intensified Smallpox Eradication

Use of Vaccinia Virus as a Vector for Other Genes

The large genome of vaccinia virus contains a substantial amount of redundant DNA, as judged by the ability of mutants which have undergone large deletions to replicate in cultured cells and in animals (see Chapter 2). Furthermore, recombination and marker rescue occur in doubly infected cells. These properties opened the way for the construction of vaccinia virus hybrids, which contain genes for specified polypeptides of other viruses, bacteria or protozoa.

Several methods have been used to construct such hybrids. One method of general applicability (Mackett et al., 1984) is to construct plasmid vectors which contain the vaccinia virus thymidine kinase (TK) gene interrupted by selected restriction endonuclease cleavage sites placed adjacent to an appropriate promoter. The continuous coding sequence for a foreign (non-vaccinial) protein is then inserted in the TK gene plasmid so that the transcriptional start site of the vaccinia promoter is adjacent to that of the foreign gene. Cells in which vaccinia virus is replicating are then transfected with this plasmid, and homologous recombination takes place at the vaccinia TK gene. Since these recombinants are TK-negative, they can be readily selected and then tested for the presence and expression of the foreign gene.

Genes for antigens which play a role in protective immunity against several important viral diseases were tested in 1983 and 1984 and a high level of expression was found in both cultured cells and laboratory animals. This method has considerable potential for providing cheap and effective vaccination against several different human diseases that are common in developing countries, as well as against some diseases of domestic animals.

Programme had begun in 1967. Many features were common to the periods before and after 1967, but that year marked a turning-point, in that the global efforts to eradicate the disease necessitated modifications in production methods and in quality control of the vaccine, and also in vaccination techniques. In this chapter, unless otherwise specified, "vaccine" means the freeze-dried smallpox vaccine.

VACCINE REQUIREMENTS FOR THE INTENSIFIED SMALLPOX ERADICATION PROGRAMME

Providing the Finance

The Intensified Smallpox Eradication Programme was launched in 1967 after the Nineteenth World Health Assembly in 1966 had voted an allocation of US$2.4 million from the WHO regular budget. It was estimated that approximately 300 million persons would have to be vaccinated annually in the endemic and adjacent countries. At 1–2 US cents per dose, this would have cost US$3–6 million for the vaccine alone, if WHO had provided all the vaccine required. Three other sources of vaccine were, however, already available: (1) several of the endemic countries were producing large amounts of vaccine for local use; (2) following a resolution of the Twelfth World Health Assembly in 1959, a few producer countries were already making donations to WHO; and (3) vaccine was being supplied to developing countries through a number of bilateral aid programmes. WHO therefore decided that vaccine additional to that produced by the endemic countries or provided through bilateral aid and necessary for the implementation of the global smallpox eradication programme should be supplied entirely by voluntary donations. The annual allocation for smallpox eradication in the WHO regular budget could then be used exclusively for technical assistance: consultants, training, research and certain supplies and equipment including transport. This policy was retained throughout the Intensified Smallpox Eradication Programme. At the time (1967) it was thought that donated vaccine would constitute a relatively small proportion of the total requirement—namely, that needed to close the gap between the perceived need and available supplies. As the present chapter relates, the actual situation was found to be much more complex and difficult.

Donations of Vaccine, 1958–1966

Apart from encouraging the establishment of national smallpox eradication programmes, the only important consequence of the resolution on global smallpox eradication adopted by the Twelfth World Health Assembly in 1959 (see Chapter 9) was the initiation of donations of smallpox vaccine, both to WHO and on a larger scale in bilateral assistance programmes. Between 1958 and 1966 the vaccine donated to WHO totalled 47 062 500 doses (from Jordan, Madagascar, Mexico, the Netherlands, the Philippines, Switzerland, Thailand, the USSR and the United Kingdom). Of this amount, 25 million doses of vaccine had been pledged by the government of the USSR in 1958 when it proposed that WHO should undertake a global smallpox eradication programme; they were delivered between 1960 and 1964. In bilateral donations between 1961 and 1966 the USSR also provided some 700 million doses of vaccine, which met the annual requirements of Afghanistan, Burma, India and some other countries during this period.

Shortfalls in Vaccine—Quality and Quantity

Since, although smallpox vaccine had been in use since 1800, standardized vaccine production procedures and reliable assay methods for quality control were not developed until the 1950s (see Chapter 7), the quality of the vaccine varied significantly in different countries. Although the quality of vaccines donated to WHO had been tested since 1959, until 1967 such vaccines accounted for an average of only 7 million doses per year (Table 11.1), or less than 2% of the vaccine needed in endemic countries. The remaining vaccine was provided by domestic production or through bilateral aid programmes and by a number of producers who sold vaccine to the endemic countries. The titre of most of these vaccines was unknown to WHO and, even when known, the tests used to determine it were of uncertain reliability and conducted mainly by the production laboratories themselves. In many laboratories, the potency was tested by vaccinating 10 children and determining the proportion of takes, or by using the rabbit skin scarification method, which was imprecise; in addition, few laboratories tested the vaccine for heat stability.

Thus WHO was faced, not with the relatively small problem of closing a gap between the total requirement and supplies obtained from existing vaccine donors and local production of vaccine in the endemic countries, but with the much larger task of developing a production–donation system to serve most of the endemic countries and their neighbours.

Table 11.1. Quantities of smallpox vaccine distributed through WHO, 1958–1979

Year	Doses of vaccine (thousands)		
	Received	Distributed	Balance at end of year
1958	25 000	0	0
1959	0	0	0
1960	5 000	3 355	0
1961	2 000	7 420	0
1962	0	9 390	0
1963	98	7 528	0
1964	9 519	13 465	0
1965	1 637	1 897	0
1966	3 808	3 808	0
1967	15 820	14 807	1 208
1968	24 949	21 316	4 842
1969	21 370	20 686	5 526
1970	29 264	32 234	2 557
1971	51 544	44 741	9 360
1972	44 816	44 593	9 683
1973	52 023	34 676	26 930
1974	40 436	44 802	22 561
1975	33 841	36 310	20 092
1976	38 456	21 822	36 727
1977	6 408	23 657	18 935
1978	9 958	16 308	13 085
1979	35 090	4 940	43 235

As is shown in Table 11.1, vaccine donations to WHO were substantially increased after the Intensified Smallpox Eradication Programme was initiated in 1967. In the early days of the programme, one of the difficulties in increasing the amounts donated was that laboratories producing smallpox vaccine in most countries had only a limited capacity that was barely enough to meet their national programme requirements, let alone help to supply the very much larger amounts of vaccine needed for a global eradication programme.

Before 1967 provisions for testing the vaccine were complicated and slow, arrangements for shipping vaccine from the producers to the recipient country were complex and resulted in many delays, and WHO had no access to reserve supplies of vaccine for immediate shipment in an emergency. The problem was overcome when distribution was centralized through the Smallpox Eradication unit in Geneva.

WHO SURVEY OF VACCINE PRODUCERS

Faced with the problems of meeting the basic requirement for smallpox eradication—namely, adequate amounts of a potent and stable vaccine and a system for distributing it to the countries in which it was needed—the Smallpox Eradication unit decided to conduct a survey of vaccine producers throughout the world. The objective was to gather information on the quality of the smallpox vaccines then in use and on the production capacity, production methods and the kind of quality control practised in different countries. This would provide a factual basis for introducing into vaccine production and use the changes needed to ensure that sufficient quantities of vaccine of suitable quality were available for the global eradication programme. Arita, then medical officer with the unit, took primary responsibility for this task.

In February 1967 the unit tried to identify all present or planned production facilities for freeze-dried vaccine and dispatched questionnaires (Plate 11.1) to the laboratories concerned, requesting information on the method of freeze-drying, the strain of vaccinia virus used, the method of growing the virus, the number of doses per vial or ampoule, and the results of testing. Of 77 laboratories contacted in 52 countries, 59 in 44 countries replied (Table 11.2). The information obtained by means of the survey is summarized below.

Methods of Vaccine Production

In 51 of the 59 laboratories, vaccinia virus was harvested from the skin of calves (39) or sheep (12); 6 laboratories were producing vaccine from water-buffaloes, 3 on the chorioallantoic (CA) membrane of chick embryos

Table 11.2. WHO survey, 1967: numbers of laboratories throughout the world producing freeze-dried smallpox vaccine, and numbers responding to the WHO questionnaire

Country or area	Number of laboratories	
	Total	Number supplying information to WHO
Africa		
Angola	1	–
Algeria	1	1
Ethiopia	1	1
Egypt	1	1
Kenya	1	1
Mozambique	1	–
Nigeria	1	1
Rwanda	1	1
South Africa	1	–
Tunisia	1	1
Zaire	1	1
Total	11	8
Americas		
Argentina	1	1
Bolivia	1	–
Brazil	4	4
Canada	2	2
Chile	1	1
Colombia	1	1
Ecuador	1	–
Peru	1	–
USA	3	3
Venezuela	1	1
Total	16	13
Asia and Oceania		
Australia	1	1
Bangladesh	1	–
Burma	1	1
China (Province of Taiwan)	1	1
Democratic Kampuchea	1	1
India	4	4
Indonesia	1	1
Iran	1	1
Iraq	1	1
Japan	6	1
New Zealand	1	1
Philippines	1	1
Syrian Arab Republic	1	1
Thailand	1	1
Total	22	16
Europe		
Austria	1	1
Belgium	1	1
Bulgaria	1	1
Czechoslovakia	1	1
Finland	1	1
France	3	3
Germany, Federal Republic of	3	3
Hungary	1	1
Italy	3	3
Netherlands	1	1
Portugal	1	1
Sweden	1	–
Switzerland	1	1
Turkey	1	1
USSR	6	1
United Kingdom	1	1
Yugoslavia	1	1
Total	28	22

FREEZE-DRIED SMALLPOX VACCINE PRODUCTION IN INDIVIDUAL LABORATORIES

1. LABORATORY PRODUCING FREEZE-DRIED SMALLPOX VACCINE

1.1. Name of Laboratory: The Medical Research Laboratory, Nairobi, Kenya

1.2. Address: P.O. Box 30141, Nairobi, Kenya

1.3. Name of Director: Dr. M.G.Rogoff

1.4. Name of person directly responsible for production: Dr. G.L.Timms

2. EQUIPMENT FOR PRODUCTION

	Make and Model Designation	Quantity
2.1. Freeze-drier	Edwards 30.P.2.T.S.	1

2.2. Type of container of final product: Ampoule hermetically sealed ☑ Vials with rubber stopper ☐ Other ☐

If other, please specify: —

3. PRODUCTION

	Type and brief history of origin
3.1. Strain of virus for seed lot	Lister Institute, Elstree, Herts, England

3.2. Vaccine produced:

in the skin of living animals ☑ Specify kind of animal: Sheep

in the chick embryo ☐

in tissue culture ☐ Specify the kind of tissue culture: —

3.3. Number of doses in each final container*: 10 20 25 50 100 Other —

4. RESULTS OF TESTING ON THE LAST THREE SUCCESSIVE FILLING LOTS (FINAL LOTS) OF VACCINE**

Filling Lot No.	Potency (PFU) at 4°C	Potency (PFU) at 37°C after 4 weeks	Bacterial counts/ml
FD 18	5.6×10^8	1.8×10^8	100
FD 19	5.5×10^8	1.5×10^8	300
FD 20	6.3×10^8	1.2×10^8	300

If any problems related to WHO requirements, please specify: —

5. DOSES OF VACCINE PRODUCED IN 1966: None doses. No. of filling lots —

6. POTENTIAL PRODUCTION CAPACITY UNDER PRESENT CONDITIONS: 10,000,000 doses annually

7. REMARKS: Samples are not yet available as we await manufacture and delivery of cartons in which to pack ampoules of vaccine and diluent.

* Please attach 3 samples of each package with diluent.

** Tests noted are detailed in WHO Technical Report Series No. 323, Smallpox Vaccine, Part A, 3.3.4; 3.3.5; 5.2.1; 5.5.

SE/67.4

Plate 11.1. Sample questionnaire circulated by the Smallpox Eradication unit in 1967 to all identified smallpox vaccine producers in countries accessible to WHO.

Table 11.3. WHO survey, 1967: vaccinifer or medium used for vaccine production

Continent	Number of producers reporting	Calf	Sheep	Water-buffalo	Chick embryo	Tissue culture
Africa	8	4	3	1	–	–
Americas	13	10	–	–	3	–
Asia and Oceania	16	7	4	5	–	–
Europe	22	18[a]	5[a]	–	–	3[a]
Total	59	39[a]	12[a]	6	3	3[a]

[a] One laboratory employed both calves and sheep as vaccinifers as well as cultured bovine embryo fibroblasts, while 2 employed calves and bovine embryo fibroblasts.

Table 11.4. WHO survey, 1967: strains of vaccinia virus used for vaccine production

Continent	Number of producers reporting	Strain used					
		Lister	New York City Board of Health	Paris	Bern	Other[a]	Unknown
Africa	8	3	–	1	–	3	1
Americas	13	3	7	2	–	1	–
Asia and Oceania	16	10	–	2	–	1	3
Europe	22	7	–	2	3	8	2
Total	59	23	7	7	3	13	6

[a] Includes the following strains: Aosta, Bohemia, Bordeaux, Chambon, Hamburg, Ikeda, Massachusetts 999, Vienna.

and 3 in tissue culture (bovine embryo fibroblasts). These results confirmed that smallpox vaccine of animal skin origin was by far the most extensively used throughout the world, in both developed and developing countries (Table 11.3).

Lyophilization equipment used in the different laboratories had been produced by at least 11 different manufacturers—in Czechoslovakia, France, the German Democratic Republic, the Federal Republic of Germany, Japan, the United Kingdom and the USA.

Strains of Vaccinia Virus

Many different strains of vaccinia virus were in use for vaccine production, although it is probable that some of these had a common ancestry. Of the 59 laboratories that responded, 23 employed the Lister strain, 7 the New York City Board of Health strain, and 7 the Paris strain. The remaining 22 laboratories used a number of different strains, none of which was used by more than 3 laboratories (Table 11.4). Furthermore, it was doubtful whether all the strains were correctly described. For example, in a laboratory in Africa it was found that the strain used was a mixture of vaccinia and cowpox viruses. Moreover, the different passage histories of what were nominally the same strains of vaccinia virus undoubtedly resulted in substantial differences in their biological properties.

Number of Doses per Container

In most countries there was, in general, little communication between those producing vaccine and those administering it in the field. Government laboratories were called on to produce a specified number of doses of smallpox vaccine each year, and the producers found it much less expensive to dry the vaccine in large ampoules. Likewise, commercial producers, who sold vaccine by the dose, preferred to package it in large containers. Few producers understood the logistic

problem that this posed for field staff, nor did they consider that, after reconstitution, much of the vaccine in large ampoules might be kept for a long time before being used (and thus lose potency), or else be discarded.

Ampoules and vials of various sizes were used in the different laboratories. Most producers regarded a "dose" as being 0.01 ml of reconstituted vaccine. About one-third of the laboratories supplied vaccine in containers of 2 or more different sizes, holding from 10 to more than 500 doses. More than 70% of vials on which the number of doses was indicated contained 100 doses or more.

Initial Potency

Information was requested from each laboratory on the initial potency, heat stability and bacterial counts of the last 3 batches of vaccine produced. Of the 59 laboratories, only 31 reported that the initial potency of the vaccine met WHO standards (see Chapter 7) in all 3 production batches on which they were asked to report (Table 11.5). Even this figure may have been an overestimate, since the assays were carried out in the production laboratories and were not independently verified. In 48 laboratories, potency was measured on the CA membrane, 1.0×10^8 pock-forming units per ml or higher being regarded as a satisfactory titre. Of these 48 laboratories, 2 recorded the potency in such a manner as to suggest that this assay procedure was not well understood, while 5 recorded results determined by the rabbit scarification technique, which was much less accurate than pock counting on the CA membrane.

Heat Stability

The results of tests to determine the heat stability of the vaccine were much less satisfactory than those for initial potency, although heat stability was very important since most of the vaccine required for the global smallpox eradication programme was to be used in tropical regions. Only 16 out of 59 laboratories recorded satisfactory results for all lots tested (titre of not less than $10^{8.0}$ pock-forming units per ml after incubation of dried vaccine at 37 °C for 4 weeks); 23 laboratories reported some or all lots to be unsatisfactory (Table 11.6), while 15 failed to report on heat stability, probably because the necessary tests were never carried out. Of the batches with unsatisfactory heat stability, the

Table 11.5. WHO survey, 1967: initial potency of 3 production lots of vaccine

Continent	Number of producers reporting	All 3 lots satisfactory[a]	Some lots satisfactory	No lots satisfactory	Rabbit skin assay only	No report
Africa	8	4	2	1	1	–
Americas	13	6	4	1	1	1
Asia and Oceania	16	9	2	1	1	3
Europe	22	12	6	–	2	2
Total	59	31	14	3	5	6

[a] Titre of not less than $10^{8.0}$ pock-forming units.

Table 11.6. WHO survey, 1967: stability after 4 weeks at 37 °C of 3 production lots of vaccine

Continent	Number of producers reporting	All 3 lots satisfactory[a]	Some lots satisfactory	No lots satisfactory	No report
Africa	8	2	1	3	1
Americas	13	2	2	3	5
Asia and Oceania	16	5	3	1	6
Europe	22	7	5	5	3
Total	59	16	11	12	15

[a] Titre of not less than $10^{8.0}$ pock-forming units.

Table 11.7. WHO survey, 1967: bacterial content[a] of vaccines

Continent	Number of producers reporting	Number of batches	Bacterial count per ml				
			0	1–9	10–99	100–499	⩾500[b]
Africa	8	19	2	–	2	12	3
Americas	12	31	22	2	2	2	3
Asia and Oceania	13	33	7	3	10	10	3
Europe	20	55	19	5	14	14	3
Total	53	138	50	10	28	38	12

[a] Viable non-pathogenic bacteria.
[b] Unacceptable by WHO standards.

titre of about half was reduced to less than $10^{7.5}$ pock-forming units per ml after heating.

Bacterial Count

Since most smallpox vaccine was produced in animal skin, bacteriological sterility was not attainable. WHO standards required that the bacterial count should be less than 500 microorganisms per ml and that no pathogenic bacteria should be present. Satisfactory results were obtained in most laboratories (Table 11.7); of 138 batches on which reports were supplied, in only 12 was the maximum acceptable count exceeded. These came from 8 different laboratories, distributed over 4 continents. Of the 50 lots for which a bacterial plate count of zero (per ml) was recorded, 10 were produced in chick embryos or tissue culture, in 3 countries.

ESTABLISHMENT OF THE WHO REFERENCE CENTRES FOR SMALLPOX VACCINE

The results of the survey confirmed early misgivings about the quality of the vaccine being supplied for use in endemic countries. It was clear that WHO needed a mechanism for the periodic testing of vaccine supplied to the eradication programme, whether by donation to the Organization, through bilateral assistance agreements or by local production in the endemic countries.

WHO does not have laboratories attached directly to it, either at Headquarters or in the regional offices. For purposes of quality control of the vaccine, therefore, the Organization had to make contractual service agreements with appropriate laboratories whereby they would undertake to conduct specified tests.

In December 1966 the Connaught Medical Research Laboratories, University of Toronto, Canada, had accepted a contract from the WHO Regional Office for the Americas for the provision of technical services to improve the quality of smallpox vaccine being produced by laboratories in that region (see Chapter 12). The services involved included an evaluation of existing smallpox vaccine production facilities and their personnel in the region, the provision of training for production personnel, and advice on the selection of equipment necessary for the production and testing of smallpox vaccines being produced in the region. Dr Robert Wilson and Dr Paul Fenje, experts from the Connaught Laboratories, visited production laboratories in the region, especially in South America, where 11 laboratories were producing smallpox vaccine, many of them providing material that did not meet WHO standards, as judged by the survey conducted in 1967.

In 1967, similar arrangements were made by WHO with the National Institute of Public Health, Bilthoven, Netherlands, of which the Director-General was Dr Jan Spaander. The head of the vaccine laboratory was Dr Anton Hekker.

In 1969 the Connaught Laboratories were formally designated as the WHO Regional Reference Centre for Smallpox Vaccine in the Region of the Americas, and the National Institute of Public Health in Bilthoven as the WHO International Reference Centre for Smallpox Vaccine. The services provided by the International Reference Centre were as follows:

(1) To test smallpox vaccines submitted to WHO from different production laboratories.

(2) On the basis of the results of tests and special studies, to advise appropriately on the improvement of vaccine production methods.

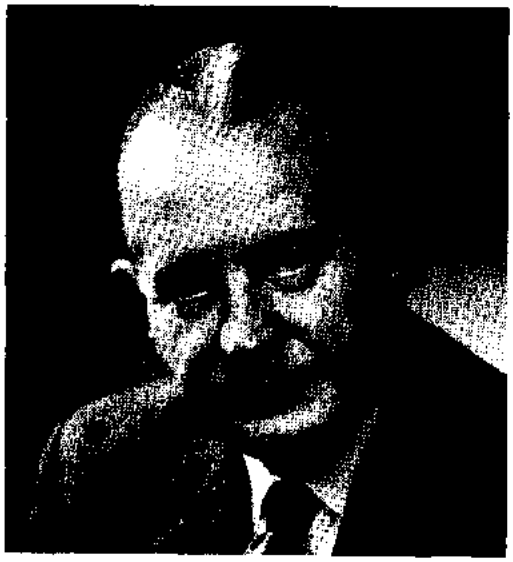
(3) To collect, maintain and study, as indicated, strains of vaccinia virus from different parts of the world.

(4) To provide seed virus and national reference vaccine when required.

(5) To conduct research which could contribute to the improvement of vaccine production and testing methodology.

(6) To train virologists in the production and testing of smallpox vaccine.

Shortly after the 1967 survey, 20 laboratories in 20 different countries submitted samples of their vaccines to the WHO International Reference Centre for Smallpox Vaccine for testing. They included 4 laboratories in Asia, 8 in Europe, 3 in North Africa, 1 in south-western Asia, 3 in sub-Saharan Africa and 1 in the USA. The samples from 6 of these laboratories were intended for use in the eradication programme, through donation to WHO or bilateral assistance; the samples from the other 14 laboratories were from experimental production runs. It is reasonable to assume that most laboratories submitted samples that they expected would meet WHO standards.



CONNAUGHT LABORATORIES, TORONTO, 1966

Plate 11.2. Robert James Wilson (b. 1915) was director of the WHO Reference Centre for Smallpox Vaccine for the Americas, located in the Connaught Medical Research Laboratories, University of Toronto, Canada.

1968

Plate 11.3. Jan Spaander (b. 1914). Director-General of the National Institute of Public Health in Bilthoven, Netherlands, 1950–1980. He greatly facilitated the operations of the WHO International Reference Centre for Smallpox Vaccine established in the Institute.

Of the 35 batches actually proposed for use in the eradication programme, 22 failed to meet the initial potency or heat-stability requirements (Table 11.8). Some of these were from potential donors in the industrialized countries. Of the 39 batches submitted by producers intending to develop freeze-dried vaccine for use in their own countries or as a contribution to the global eradication programme, 25 failed to meet the WHO requirements. The conclusion was that in 1967 not more than 10% of the vaccine in use in endemic countries met WHO requirements, while the quality of the experimental batches was equally unsatisfactory.

DEVELOPMENT OF IMPROVED VACCINES

The results of the survey, together with those of other tests on samples carried out by the WHO reference centres, indicated the urgency of strengthening vaccine production

Table 11.8. Independent testing in 1967 by the WHO International Reference Centre for Smallpox Vaccine in Bilthoven of production batches intended for use in the eradication programme or in experimental production[a]

Continent	Proposed for use in the eradication programme through donation to WHO or through bilateral contributions			Experimental production batches		
	Number of producers	Number of batches tested	Number of batches unsatisfactory[b]	Number of producers	Number of batches tested	Number of batches unsatisfactory[a]
Americas	1	1	1	0	0	0
Africa	1	1	0	5	21	19
Asia	2	11	9	3	6	4
Europe	2	22	12	6	12	2
Total	6	35	22	14	39	25

[a] In this and later tables, the designation of results as "satisfactory" or "unsatisfactory" was based on the following criteria for a satisfactory product (titres expressed in pock-forming units per ml):

Initial potency: $\geqslant 10^{8.0}$
Heat stability, titre after 4 weeks at 37 °C: $\geqslant 10^{8.0}$
Bacterial count (colonies per ml): < 500

[b] Failed to meet WHO requirements in terms of initial potency or heat stability.

methods and quality control so that potent, heat-stable vaccine could be made available to the global programme.

A number of steps were therefore taken by the Smallpox Eradication unit to improve the quality of the vaccine and to ensure an adequate supply:

(1) organization of a Travelling Seminar on Vaccine Production in March 1968, which resulted in the production of a WHO document on production methodology;
(2) arrangement of visits to production laboratories by WHO programme staff and consultants;
(3) establishment of a reference vaccine;
(4) production of seed lots of Lister strain vaccine by the WHO International Reference Centre for Smallpox Vaccine;
(5) development of a rapid heat-stability test for the vaccine; and
(6) regular checking of vaccine potency and heat stability by the WHO reference centres.

Meeting of Experts (March 1968)

Although the basic principles of vaccine production and testing had already been described in two issues of the WHO Technical Report Series (WHO Study Group on Requirements for Smallpox Vaccine, 1959; WHO Expert Group on Requirements for Biological Substances, 1966), the steps in the production of smallpox vaccine had mostly been empirically developed. Little specific information about production methods had been published in the scientific literature. Furthermore, the survey had shown that unsatisfactory batches of vaccine were being produced in laboratories in developed and developing countries alike.

WHO usually handled such problems by arranging for a well-qualified consultant to visit and advise the appropriate institutions, in this case the producers whose vaccine had been found to be unsatisfactory. However, since there were then at least 20 producers supplying vaccine of substandard quality, it was difficult to recruit consultants who had the requisite experience and skills in the technical procedures and production management, and who would be able to devote the necessary time to such an operation. These considerations led the Smallpox Eradication unit to conclude that a better way to improve vaccine production rapidly would be to prepare a manual on the production of freeze-dried smallpox vaccine that would describe the simplest possible procedures for all stages of production and testing of a potent, stable and safe vaccine.

Development by WHO of Quality Control of Smallpox Vaccine

In 1958 a resolution of the Eleventh World Health Assembly had stressed the importance of "thermostable smallpox vaccine" for use in tropical areas, and in 1962 the Fourteenth World Health Assembly invited countries to contribute freeze-dried vaccine to the WHO eradication programme. Thus WHO had to test donated vaccine before accepting it and began to do so in 1962. However, the arrangements did not cover other, much larger, amounts of vaccine being donated through bilateral assistance programmes or vaccine being produced in endemic countries for national programmes. In fact, the WHO Secretariat held the view that bilateral contributions and the way that they were used were the concern solely of the two countries involved, and that WHO should not intervene and had no authority to impose international quality control on domestic vaccine producers. These problems were addressed after the 1967 survey revealed that so many producers, in so many countries, were producing substandard vaccine. Using these data, the Smallpox Eradication unit initiated a continuing exchange of information with individual producers, who came to understand the importance of international quality control.

Another consequence of the WHO survey of vaccine quality was that the results led governments of many countries to recognize the deficiencies of the system by which producers themselves evaluated the quality of their products, and thus helped in the establishment in several countries of independent systems for the quality control of all biological products.

Panel of experts

Selected experts from the following laboratories were chosen to participate in a seminar held in Geneva in March 1968 and in activities related to the preparation of the manual on vaccine production:

Connaught Medical Research Laboratories, University of Toronto, Toronto, Canada

Moscow Research Institute for Viral Preparations, Moscow, USSR

National Institute of Public Health, Bilthoven, Netherlands

Research Institute of Immunology, Prague, Czechoslovakia

Wyeth Laboratories, Philadelphia, USA

At that time the first and the third laboratories were directly assisting the WHO eradication programme in testing vaccine samples; the fourth laboratory—in Prague—had published an important developmental study on smallpox vaccine; and the laboratories in the USSR and the USA were major producers of freeze-dried smallpox vaccine for the global eradication programme.

In the 1960s the Lister Institute, in the United Kingdom, was the leading laboratory in the technology of freeze-dried smallpox vaccine (see Chapter 7). Because funds for its research were derived partly from the proceeds of the sale of its vaccine, the Institute turned down WHO's request to permit the participants in the seminar to visit the Institute, believing that the full disclosure of its technical knowledge might reveal trade secrets. However, the Director of the Lister Institute agreed to the appointment of Dr Colin Kaplan, then Director of its Vaccine Production Department, as a special consultant to the group. Early in 1968 exploratory discussions were held in Bilthoven between Dr Kaplan, Dr A. C. Hekker (Bilthoven), and Henderson and Arita (WHO), and a working paper on production methods, based mainly on those used in the Lister Institute, was prepared as a basis for discussions on the proposed manual.

First meeting (19–23 March 1968)

The first meeting of the group of experts, held at WHO Headquarters in Geneva, reviewed various aspects of production and testing. Working papers submitted by the participants provided information from each laboratory on the following topics: nature of seed lot used for production, virus titre at each

production stage from seed lot to final product, virus yield, heat-stability studies of final product, and level of bacterial contamination at various stages of production. Photographs showing the various production processes were examined, with a view to their inclusion in the proposed manual.

Visits to laboratories and final meeting (28–30 March 1968)

Immediately after the first meeting, the group of experts visited the Moscow Research Institute for Viral Preparations and Wyeth Laboratories, Philadelphia, two of the major vaccine contributors, to observe the production process and examine the production data. The final meeting was held at Wyeth Laboratories. The draft of the manual on the methodology of vaccine production was carefully reviewed in the light of the visits. Agreement was reached on a document entitled *Methodology of Freeze-dried Smallpox Vaccine Production*, the first report to describe simple and practical methods for the production and testing of freeze-dried vaccine. Although never officially published, it contained all the necessary information at a level of detail not provided elsewhere and was made widely available as a document of the Smallpox Eradication unit (SE/68.3 Rev. 2), being distributed to all laboratories interested in the production of freeze-dried smallpox vaccine. Its contents are summarized below.

Production of Freeze-dried Vaccine

Choice of vaccinifer

Although in 1968 the successful production of smallpox vaccine in chick embryos

WYETH LABORATORIES

Plate 11.4. Members of the Seminar on Vaccine Production, at the final meeting from 28 to 30 March 1968, at the Wyeth Laboratories, Philadelphia, Pennsylvania, USA. *Left to right, front row:* P. Fenje (Canada), S.S. Marennikova (USSR), A.C. Hekker (Netherlands), J.H. Brown (USA), R.J. Wilson (Canada) and I. Arita (WHO); *back row:* F.M. McCarthy (USA), M.Z. Bierly (USA), H. Tint (USA), V.N. Milushin (USSR), A. Bernstein (USA), C. Kaplan (United Kingdom), D.A. Henderson (WHO), B.A. Rubin (USA) and A.K. Fontes (USA).

and in cultured cells had been reported, it was decided that the document should concern itself only with the traditional method, in which animal skin was used for the production of vaccine pulp, since this was far simpler and more straightforward. It was thought better to upgrade the method familiar to producers in developing countries than to suggest techniques that were comparatively new and that failed at that time to give a product of satisfactory heat stability.

Strain of vaccinia virus

It was recommended that a strain of vaccinia virus should be used which would induce adequate immunity in man with as few ill effects as possible, that it should produce compact, clearly visible white pocks on the chorioallantoic membrane, thus making assay easier, and that unsuitable strains should be discarded. No particular strain was officially recommended but, in response to inquiries, the Smallpox Eradication unit advised that either the Lister or the New York City Board of Health strain should be used. The Lister strain was more widely used, because it produced pocks on the CA membrane that were easier to count and because the WHO International Reference Centre later produced seed lots of this strain for distribution to vaccine producers in developing countries (see below).

Seed lots

The principle of using seed lots (WHO Study Group on Requirements for Smallpox

Plate 11.5. **A:** Vaccine production in calf skin in Bangladesh, using the scarifier developed by Wyeth Laboratories, Philadelphia, Pennsylvania, USA. **B:** Enlarged view of scarifier.

Vaccine, 1959; see Chapter 7) was recommended and a practical method for preparing them was described. Slonim et al. (1969) showed that the viral concentration in the harvested pulp was 3 times higher when vaccinifers were scarified with an inoculum containing $10^{8.3}$ pock-forming units per ml than with one containing 10^{7} pock-forming units per ml. To provide a safety margin, the document stipulated that the titre of the seed lot should not be less than $10^{8.7}$ pock-forming units per ml. This was substantially higher than the acceptable titre for vaccination, but was essential if adequate yields of high-titre vaccine were to be obtained.

Preparation of vaccinifer

A rigorous schedule for cleansing the animal skin was recommended, which substantially reduced the bacterial count to the extent that very few or no viable bacteria (and no pathogens) were found in the aliquot of vaccine (usually 1 ml) cultured.

Scarification

The recommended method of scarification was based on the experience of the participating producers, and an instrument for scarification of the vaccinifer in use in Wyeth Laboratories was produced by WHO and distributed to producers on request (Plate 11.5).

Preparation of vaccine

The method of extraction and treatment of the viral suspension was described with special reference to the specification of the required potency at each stage of the production. Phenol was added to a concentration of 0.5% by weight, following observations by Hekker & van Ramshorst (1969), who had investigated the phenol content and bacterial counts of 51 lots of freeze-dried vaccine from 23 laboratories in several countries and shown that this was the maximum concentration that would reduce the bacterial count without affecting initial potency or heat stability.

Before being dispensed into ampoules, the viral suspension was required to have a titre of at least $10^{8.7}$ pock-forming units per ml, since the processes of freeze-drying and incubation at 37 °C for 4 weeks would somewhat reduce its potency. The final vaccine, after incubation, was required to have a titre of not less than 10^{8} pock-forming units per ml, in line with the standards established by WHO in 1965.

Size of container used for vaccine distribution

The volume of fluid to be dispensed into each final container was specified as between 0.15 ml and 0.25 ml, which would provide 15–25 doses per ampoule by the conventional scarification or multiple pressure techniques and 60–100 doses for vaccination with the bifurcated needle. Although ampoules providing fewer doses were requested by field workers, production experts agreed that 0.15-ml lots were the smallest practicable volumes that could be dispensed and dried.

Reconstituting fluid

Traditionally, glycerol had been used at a concentration of 40–60% in the suspending fluid of liquid vaccines. It had to be omitted from the fluid used to suspend the lymph for freeze-drying, but its properties made it useful for the reconstituted vaccine. Studies by Slonim & Röslerová (1969) showed that, at

1984

Plate 11.6. Dimitrij Slonim (b. 1925), of the Institute of Sera and Vaccines, Prague, Czechoslovakia, contributed to methods for the accurate assay of vaccine and was a member of the Seminar on Vaccine Production.

temperatures above 0 °C, glycerol inactivated vaccinia virus at a rate that was proportional to temperature and glycerol concentration. It was suggested in the document that the reconstituting fluid should consist of a solution of 50% (v/v) glycerol in 0.004 M McIlvaine's buffer.

Freeze-drying equipment

The document provided advice on the advantages and disadvantages of the different types of freeze-drier available commercially (centrifugal and shelf; Plate 11.7), and the ampoules, vials and rubber stoppers appropriate for them.

CONTINUING QUALITY CONTROL OF SMALLPOX VACCINE

Having established methods for the production of smallpox vaccine suitable for use in tropical countries, it was important that both WHO and national authorities should continue to test the vaccine provided, whether donated through WHO or through bilateral assistance or produced locally in the endemic countries.

Testing Samples of Vaccine

Between 1959 and 1967 the testing of samples of vaccine donated to WHO was a

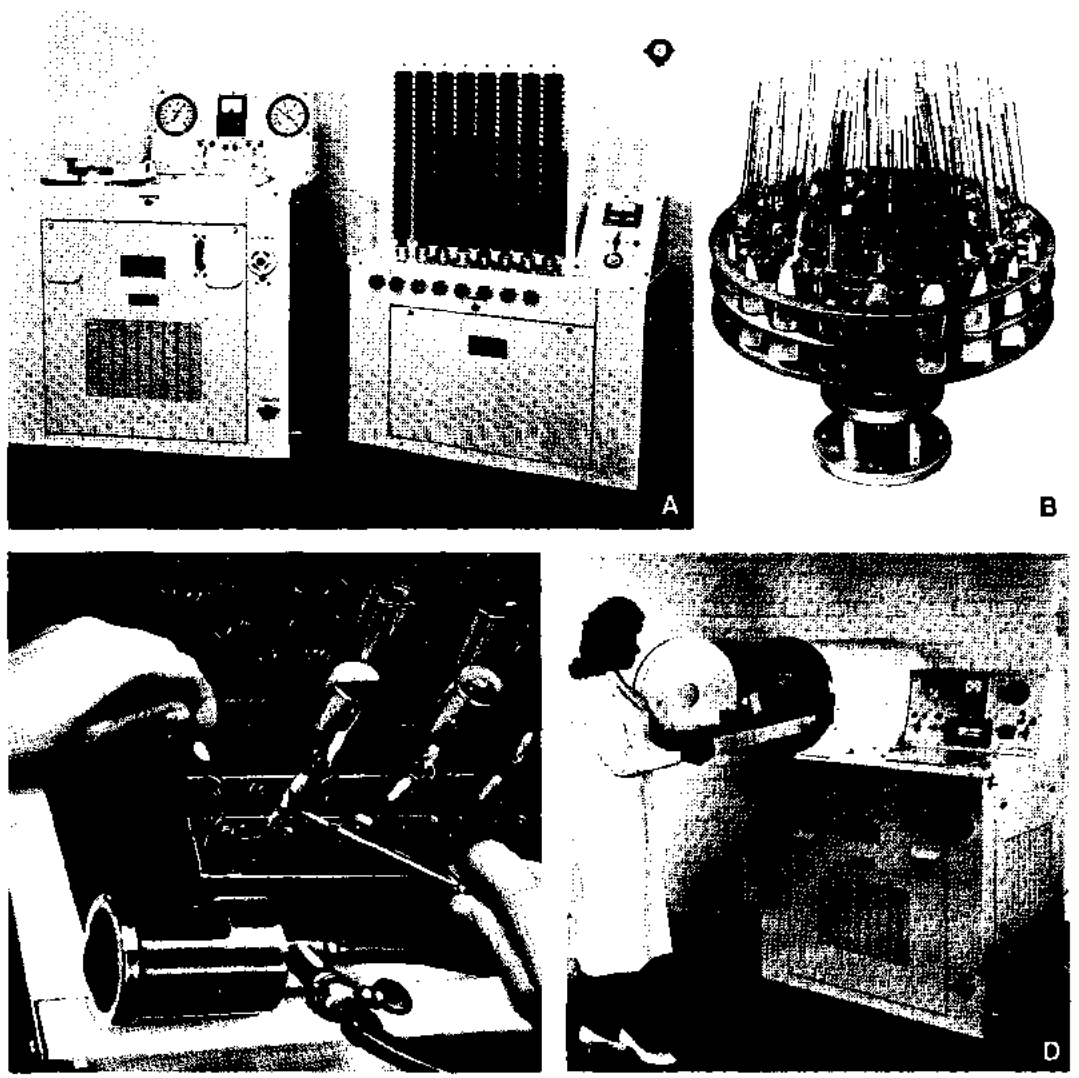


Plate 11.7. Freeze-driers of the type used for the manufacture of smallpox vaccine. **A:** Centrifugal freeze-drier and secondary drier, with manifolds. **B:** Centrifugal carrier plate assembly. **C:** Sealing headers for ampoules on secondary drier. **D:** Shelf-type freeze-drier.

lengthy process, sometimes more than a year elapsing between the submission of a sample and the sending of a report on its potency to the producer. Two factors contributed to this delay. First, the testing arrangements were entrusted as additional work to the small Biological Standardization unit of WHO, whose normal duties involved the staff in frequent absences from Geneva; samples for testing and reports on potency had to await their return from duty travel. Secondly, the testing was carried out for WHO by the State Serum Institute in Copenhagen, which produced smallpox vaccine on a relatively small scale and for only a brief period each year; to rationalize its work, it usually tested samples from WHO at the same time as its own local production batches. This delay, which was unacceptable if the assays of vaccine quality were to be of any use, was eliminated when the responsibility for testing was transferred to the WHO reference centres for smallpox vaccine and the handling of samples and reports in Geneva was taken over by the Smallpox Eradication unit.

After 1968, all producers who donated vaccine to the eradication programme or who produced vaccine for national eradication programmes were requested to submit vaccine samples periodically for testing by WHO. In addition, laboratories developing the capacity to produce freeze-dried vaccine were encouraged to submit samples to WHO for testing, so that they could be advised, if necessary, on how to improve the quality of their vaccine. Between 1967 and 1984, 27 countries donated freeze-dried vaccine to WHO (see Table 11.15). Samples of all these donations were sent to WHO reference centres for testing. At later stages of the programme, when samples from producers consistently met WHO requirements, donations were accepted without advance testing, although samples were tested after the donation had been received, to confirm that it was of the desired quality.

For the quality control of vaccine produced locally in endemic countries, WHO smallpox eradication staff working for national programmes were actively involved in collecting and dispatching vaccine samples and, if the results of the assays carried out by the national laboratory and the WHO International Reference Centre were in agreement, the batches of vaccine from which the samples had been taken were dispatched for use in the field.

Plate 11.8. Nelja N. Maltseva (b. 1934), a member of the WHO collaborating centre in the Moscow Research Institute for Viral Preparations, USSR, was active in laboratory diagnosis and research and worked as a consultant on vaccine production in several countries.

Visits by Consultants

Vaccine producers having problems in ensuring that vaccine quality met WHO requirements, starting new methods of production or modifying traditional production methods were encouraged to benefit from the advice of visiting WHO short-term consultants. Although many laboratories were engaged in vaccine production, only a few of the personnel concerned were sufficiently experienced to be able to suggest realistic improvements in production methods, since instruments and working procedures had to be adapted to the practical realities in developing countries. The 15 consultants and the countries they assisted are listed in Table 11.9. Over the period 1967–1979 they visited more than 20 laboratories.

Freeze-driers manufactured by Edwards High Vacuum, Crawley, Sussex, England, were widely used and, at the request of the Smallpox Eradication unit, technicians from this company visited producers to maintain and service equipment.

Reference Vaccine

The International Reference Preparation of Smallpox Vaccine was established in 1962

Table 11.9. WHO short-term consultants and countries visited, 1967–1974

Name	Laboratory or position	Countries visited
Dr P. Fenje Dr R. Wilson	Connaught Medical Research Laboratories, Toronto, Canada	South American countries (1966–1973)
Mr R. Kent	Technical Officer, WHO Regional Office for Africa	India (1967); Bangladesh (1972); Guinea (1967–1971)
Dr D. Slonim	Research Institute of Immunology, Prague, Czechoslovakia	Ethiopia (1967)
Dr C. Kaplan	Department of Microbiology, University of Reading, Reading, England	Indonesia (1968); Burma (1968); Thailand (1968); India (1969); Sri Lanka (1969 and 1971)
Dr A. Bernstein	Wyeth Laboratories, Philadelphia, Pennsylvania, USA	Iran (1968); Bangladesh (1972)
Dr R. Netter	Director-General, National Health Laboratory, Paris, France	Guinea (1969); Democratic Republic of the Congo (1969)
Dr V. Dostal	University Institute of Hygiene, Graz, Austria	Syrian Arab Republic (1969); Iraq (1969); Jordan (1969)
Dr J. Espmark	National Bacteriological Laboratory, Stockholm, Sweden	Brazil (1969)
Dr P. Tuchinda	Ministry of Public Health, Bangkok, Thailand	Syrian Arab Republic (1969); Jordan (1969)
Mr R. Grundon	Lister Institute of Preventive Medicine, Elstree, England	Bangladesh (1970)
Dr K. Dumbell	Department of Virology, St Mary's Hospital Medical School, London, England	Malaysia (1971); Bangladesh (1974); India (1974)
Dr N. Maltseva	Moscow Research Institute for Viral Preparations, Moscow, USSR	Egypt (1972); Syrian Arab Republic (1972 and 1973); Iran (1972); Iraq (1972 and 1973)
Dr S. Shekhkhina	Moscow Research Institute for Viral Preparations, Moscow, USSR	India (1973)
Dr A. Hekker	National Institute of Public Health, Bilthoven, Netherlands	Indonesia (1973)

(Krag & Bentzon, 1963) and is held in the custody of the International Laboratory for Biological Standards, State Serum Institute, Copenhagen, Denmark. One ampoule contains 14 mg of freeze-dried vaccine. This International Reference Preparation was designed to be used for standardizing producers' own reference vaccines, which could then be used whenever testing was carried out. However, many producers, especially in developing countries, were unable to produce satisfactory working reference vaccines. The WHO International Reference Centre for Smallpox Vaccine therefore produced a special batch of freeze-dried vaccine, No. 6713-18, which had been titrated in parallel with the International Reference Preparation and had a titre of 10^8 pock-forming units per ml when reconstituted. A number of these ampoules were kept in Geneva at −15 °C and the rest at the WHO International Reference Centre; they were provided as required to vaccine producers in developing countries for use as reference vaccines.

Seed Lots of Vaccine

It was recommended in the document *Methodology of Freeze-dried Smallpox Vaccine Production* that the seed lot system should be used (see box)—i.e., a reasonably large freeze-dried or frozen primary seed lot was to be maintained, from which secondary seed lots to be used in production runs were to be derived. These secondary seed lots were to be no more than 5 passages removed from the primary seed lot. However, in many laboratories the history of primary seed lots was unknown, and many were of low potency (less than $10^{8.7}$ pock-forming units per ml) or were heavily contaminated, so that it was extremely difficult for certain producers to use the system.

In 1968, responding to a request from the Smallpox Eradication unit, the WHO International Reference Centre for Smallpox Vaccine overcame these difficulties by the production of a large secondary seed lot (Li_2K_2G) from the Lister strain of vaccinia virus. This consisted of a large number of ampoules of freeze-dried virus, each of which after reconstitution contained 10 ml of virus with a titre of about 10^9 pock-forming units per ml. The Lister strain of virus used in this seed lot had been received from the Lister Institute in 1961 as a sheep lymph prepara-

The Seed Lot System for Vaccine Production

"The seed virus system is one of the procedures necessary to ensure that each production lot of vaccine has the same desirable biological characteristics as the parent strain ... [It] requires that primary and several secondary seed lots be produced and dispensed in sufficient numbers of containers to ensure an adequate supply of virus for inoculation for long periods of time. The secondary seed virus used for production is not to exceed the fifth serial passage of the primary seed virus; thus, each production lot of vaccine will not be more than six passages removed from the primary seed virus.

"The size of a seed virus lot is dependent upon the requirements of the production laboratory. Units requiring large volumes of seed virus during a short interval of time may find it necessary to prepare several passages of secondary seed lots in order to obtain the required volume of inoculum for production lots of pulp. Smaller production units may be able to utilize the second passage of the primary seed as the inoculum in the production of vaccine pulp.

"The primary and secondary seed virus lots should pass the standard tests for identity, safety and bacterial content ... The potency of the primary and secondary seed virus should be as high as is practicable and assayed periodically (every three months) to ensure adequate potency following long-term storage. Seed virus with a potency less than 5×10^8 p.f.u. per ml should not be used.

"Ideally, the primary and secondary seed lots should be freeze-dried in ampoules and stored at 4 °C or lower. However, an adequate supply of potent seed virus can also be maintained by the use of freeze-dried primary seed virus and the preparation of secondary seed virus as glycerolated suspensions (50% glycerol in 0.004 M McIlvaine's buffer) which will retain adequate potency for one year when stored at −20 °C." (From *Methodology of Freeze-dried Smallpox Vaccine Production*; SE/68.3 Rev. 2.)

tion, and had been passed twice on calf skin. Second-passage material was lyophilized in 10-ml amounts as seed virus for the production of smallpox vaccine. Thus, the vaccine in the seed lots prepared for international distribution was the second passage on calf skin, and had a high viral content. These seed lots were distributed on request to producers and often used immediately for the inoculation of vaccinifers, so that the production process was accelerated. The availability of this material was partly responsible for the widespread use of the Lister strain of vaccinia virus from 1969 onwards (see Table 11.21).

These two products, the working reference vaccine and the secondary seed lot ampoules, greatly simplified procedures and assisted producers who were encountering difficulties. When supplied, they were always accompanied by special instructions on the potency testing of smallpox vaccine, as outlined below in the section on assay technique.

Evaluation of Testing Methods

Rapid heat-stability test

During the first 3 years of the Intensified Smallpox Eradication Programme, substantial efforts were made to ensure the flow of adequate supplies of vaccine to national smallpox eradication programmes. All vaccine, however, was tested in order to ensure that its quality was satisfactory. The bottleneck in the standard testing procedures was the heat-stability test, which took not less than a month, because of the need to assay the vaccine after 28 days at 37° C. Cross et al. (1957), however, had demonstrated the feasibility of determining stability by assaying potency before and after heating at 100 °C for 1 hour.

In 1969, Arita, in collaboration with the WHO International Reference Centre for Smallpox Vaccine, compared the results of

heat-stability testing of 139 batches of vaccine by the conventional 4-week test at 37 °C and the 1-hour boiling test (Fig. 11.1). Preparations with an initial titre of over $10^{8.5}$ pock-forming units per ml and a titre of more than $10^{7.5}$ pock-forming units per ml after boiling always met the standard requirements for heat stability (Arita, 1973). Accordingly, after 1969, the testing procedures at the WHO International Reference Centre were modified. Vaccine samples were first tested for stability by incubation at 100 °C for 1 hour; if the vaccine met the requirements noted, it was regarded as acceptable. Vaccine which failed to pass this screening test was further tested by the conventional heat-stability test.

This approach greatly speeded the testing procedures. Between 1969 and 1972, of 337 batches tested by this method by the WHO International Reference Centre, 224 (67%) were found to be acceptable. This method was also used in India (Sehgal et al., 1969; Sehgal & Singha, 1972). For reasons unknown, vaccine produced in Bangladesh in vials rather than ampoules and Iranian vaccine prepared in ampoules consistently failed the boiling test, although these vaccines were usually acceptable by the standard heat-stability test. They were therefore selectively tested only by the standard heat-stability method.

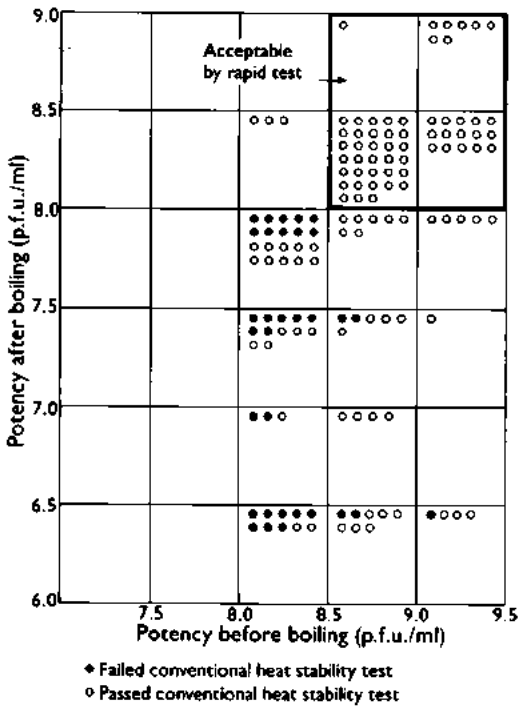


Fig. 11.1. Comparison of the rapid screening test (100 °C for 60 minutes) and the conventional heat stability test (37 °C for 4 weeks). Open circles: acceptable by conventional test; closed circles: unacceptable by conventional test. (From Arita, 1973.)

Discrepancies between test results

As the testing services developed, the Smallpox Eradication unit took great pains to determine the causes of discrepancies sometimes encountered between the results of potency tests carried out in the WHO International Reference Centre and in individual production laboratories. These investigations often led to improvements in the manufacturers' potency testing procedures and also helped to maintain their confidence in the results obtained by the centre. When a discrepancy occurred, the test was repeated in order to determine whether the difference in titres was, in fact, significant. Use of the centre's reference vaccine, which was distributed to all producers on request, also helped to solve such problems.

Assay technique

Some discrepancies resulted from apparently minor differences in the procedures used for assaying vaccine on the CA membrane. For instance, it was recommended (WHO Expert Group on Requirements for Biological Substances, 1966) that: "At least ten chick embryos, each of about 12 days' incubation, shall be divided into two equal groups. To the chorio-allantoic membrane of each embryo of the first group, 0.1 ml or 0.2 ml of a suitable dilution of the vaccine shall be applied." In this context, some producers were using 12-day-old embryonated eggs and some 13-day-old eggs, or 11-, 12- or 13-day-old eggs as available. Some producers used an inoculum of 0.1 ml, others one of 0.2 ml.

Dr Alan Bernstein (Wyeth Laboratories) studied the titre of smallpox vaccine as a function of the number of days of incubation of the embryonated eggs (10, 11, 12, 13 or 14 days). The younger the embryo used for the assay, the lower was the apparent titre of the vaccine (Table 11.10). The use of eggs only 1 day younger or 1 day older than 12 days changed the titre by as much as -0.6 to $+0.4$ log unit respectively. Differences were also observed when inocula of 0.1 and 0.2 ml were used (Slonim et al., 1967). Because of these

Table 11.10. Variation in results of titrations of vaccinia virus according to age of chick embryos at time of inoculation[a]

Length of incubation of chick embryo (days)	Sample studied										Average difference
	A		B		C		D		E		
	Titre[b]	Difference[c]	Titre[b]	Difference[c]	Titre[b]	Difference[c]	Titre[b]	Difference[c]	Titre[b]	Difference[c]	
10	7.3	−1.0			7.2	−1.0			7.1	−1.1	−1.0
11	7.9	−0.4	8.0	−0.3	7.6	−0.6	7.7	−0.6	7.7	−0.5	−0.5
12	8.3	-	8.3	-	8.2	-	8.3	-	8.2	-	-
13	8.5	+0.2	8.7	+0.4	8.4	+0.2	8.7	+0.4	8.4	+0.2	+0.3
14	8.6	+0.3	8.5	+0.2	8.4	+0.2	8.7	+0.4	8.5	+0.3	+0.3

[a] Source: A. Bernstein (personal communication, 1969).
[b] Expressed as $\log_{10}$ pock-forming units per ml.
[c] From the titre obtained with 12-day-old chick embryos.

findings, an inoculum of 0.1 ml and an incubation period of 12 days for the eggs were accepted as standard.

It was also suggested that the quality of the eggs from different geographical areas might affect the assays. For reasons unknown, vaccines assayed in developing countries often gave titres 0.2–0.3 log unit lower than when tested by the WHO reference centres, a not unwelcome circumstance, as it ensured with greater certainty that the vaccine used in the field was fully potent.

To ensure comparability of results, it has been decided that assay by pock counting on the CA membrane will be used for as long as it is necessary to test samples from the vaccine reserves held in Geneva and Lausanne (see Chapter 28).

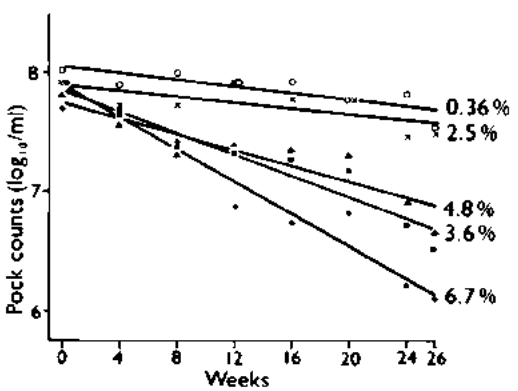


Fig. 11.2. Decline with time in titres of samples of smallpox vaccine of different moisture contents kept at 24 °C. The relative effects were comparable at 37 °C, but the decline in titre at all moisture contents higher than 0.36% was greater. (From Sparkes & Fenje, 1972.)

Moisture content

Although residual moisture appeared to be an important factor influencing the stability of freeze-dried vaccine, it was difficult to establish criteria for the moisture content. Sparkes & Fenje (1972) studied the decline with time in the potency of freeze-dried vaccine with moisture contents ranging from 0.36% to 6.7%, at temperatures of 4 °C, 24 °C, 37 °C and 100 °C (Fig. 11.2). They concluded that a residual moisture content of less than 1% was essential for the satisfactory storage of freeze-dried smallpox vaccine at ambient temperatures. However, the test for moisture content was too expensive and technically too difficult to use as a routine, and samples with too high a moisture content rarely passed the heat-stability test. The moisture content was sometimes assayed with batches of low heat stability to determine whether this was due to inadequate freeze-drying.

Improvements in Vaccine Quality

General

The Intensified Smallpox Eradication Programme marked the first time in the history of WHO that an effective world-wide quality control programme for biological products had been established (Fig. 11.3). Between 1967 and 1980, 2578 production batches were tested, the annual number of samples ranging from 392 in 1973 to 46 in 1980 (Table 11.11). From 1969 onwards there was a considerable improvement in vaccine quality. Between 1967 and 1972 initial potency was unsatisfactory in 47% of instances, heat stability in

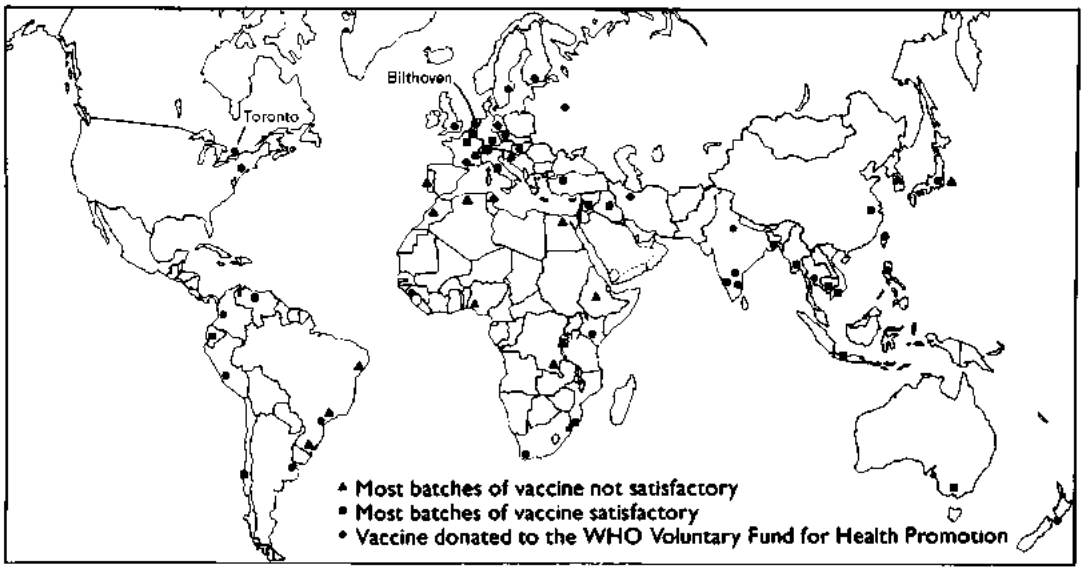

Bilthoven
Toronto
▲ Most batches of vaccine not satisfactory
• Most batches of vaccine satisfactory
• Vaccine donated to the WHO Voluntary Fund for Health Promotion

Fig. 11.3. Locations of various categories of producers of freeze-dried smallpox vaccine, 1967–1979; and of the WHO Reference Centre for Smallpox Vaccine for the Americas (Toronto) and the WHO International Reference Centre for Smallpox Vaccine (Bilthoven).

Table 11.11. WHO quality control of freeze-dried vaccine: results of tests carried out in WHO reference centres for smallpox vaccine in Bilthoven and Toronto on experimental and production batches from producers shown in Fig. 11.3

Year	Number of producers	Number of batches submitted	Number satisfactory (%)	Number unsatisfactory (%)	Unsatisfactory		
					Initial potency	Heat stability	Bacterial count
1967	20	74	27 (36)	47 (64)	32	12	8
1968	23	136	74 (54)	62 (46)	26	36	5
1969	30	164	128 (78)	36 (22)	23	12	5
1970	27	380	312 (82)	68 (18)	27	35	13
1971	32	206	154 (75)	52 (25)	31	23	5
1972	27	311	241 (77)	70 (23)	32	39	1
1973	30	392	367 (94)	25 (6)	5	20	0
1974	28	231	199 (86)	32 (14)	11	20	1
1975	21	167	139 (83)	28 (17)	15	10	6
1976	16	213	203 (95)	10 (5)	2	7	3
1977	11	114	101 (89)	13 (11)	1	12	1
1978	9	59	57 (97)	2 (3)	0	2	0
1979	10	85	82 (96)	3 (4)	3	1	0
1980	5	46	46 (100)	0 (–)	0	0	0
Total	–	2 578	2 130 (82.6)	448 (17.4)	208	229	48

43% and bacterial count in 10%. From 1973 onwards the initial potency was usually satisfactory but heat stability remained an occasional problem.

Of 1842 batches tested between 1967 and 1976 and classed as satisfactory, an average of 10% were of "borderline" potency after heating—i.e., the potency was between $10^{7.8}$ and $10^{8.0}$ pock-forming units per ml. Only one borderline batch was found after that date.

In addition to this regular quality control of vaccine provided by production laboratories, staff of national smallpox eradication programmes sent samples of vaccine from the field for testing if the expiry dates had passed, or if shipments had been delayed or mishandled so that their potency might have been adversely affected (Table 11.12). If the samples tested met the standards of potency and stability, the expiry dates for that batch were extended for another year. After 1970

Table 11.12. WHO quality control of freeze-dried vaccine used in the Intensified Smallpox Eradication Programme: results of tests carried out in WHO reference centres for smallpox vaccine in Bilthoven and Toronto on samples submitted from the field

Year	Number of producers	Number of batches submitted	Number satisfactory (%)	Number unsatisfactory	
				Initial potency	Heat stability
1967	2	3	2 (67)	1	0
1968	3	41	22 (54)	14	5
1969	6	75	51 (68)	21	3
1970	8	52	23 (44)	27	2
1971	11	32	25 (78)	7	0
1972	7	28	23 (82)	5	0
1973	3	15	11 (73)	3	1
1974	4	14	13 (93)	0	1
1975	5	15	14 (93)	0	1
1976	8	29	29 (100)	0	0
1977	7	35	33 (94)	1	1
1978	2	15	11 (73)	0	4
1979	3	14	14 (100)	0	0
1980	9	9	8 (89)	0	1
Total	-	377	279	79	19

there was a general improvement in quality, suggesting that vaccine supplies were being more carefully handled in the countries in which they were used.

Results in different regions

By 1971 the quality control operation covered 41 laboratories producing vaccine for national eradication campaigns, for donation to WHO or for bilateral assistance to endemic countries. Although there was a distinct overall improvement, problems continued to occur. Table 11.13 shows the results of quality control tests by WHO reference laboratories of batches produced during the period 1971–1974.

In South America, Brazil was the only country in which smallpox was still endemic in 1967, but the quality of the vaccine produced in 3 of its 4 production laboratories, most of which was grown in eggs, often failed

Table 11.13. WHO quality control of vaccine in use for the Intensified Smallpox Eradication Programme: results of tests carried out, by WHO region

WHO region	Number of producers	1971 Number of batches		1972 Number of batches		1973 Number of batches		1974 Number of batches	
		Tested	Satisfactory	Tested	Satisfactory	Tested	Satisfactory	Tested	Satisfactory
Africa	2[a]	5	5	32	28	2	2	24	21
Americas	11[b]	24	14	58	29	30	28	33	17
South-East Asia	8[c]	107	103	120	108	253	245	86	83
Europe	13[d]	27	21	17	15	29	27	42	38
Eastern Mediterranean	3[e]	11	4	67	54	54	49	29	29
Western Pacific	4[f]	6	6	6	6	9	9	-	-
Total	41	180	153	300	240	377	360	214	188
Satisfactory (%)		85		80		95		88	

[a] Guinea, Kenya.
[b] Argentina, Brazil (4), Canada, Colombia, Ecuador, Peru, Venezuela, USA.
[c] Bangladesh, Burma, India (4), Indonesia, Thailand.
[d] Belgium, Czechoslovakia, Finland, France, German Democratic Republic, Federal Republic of Germany, Hungary, Netherlands, Sweden, Switzerland, USSR, United Kingdom, Yugoslavia.
[e] Iran, Iraq, Syrian Arab Republic.
[f] China (Province of Taiwan), New Zealand, Philippines, Viet Nam.

to meet WHO standards, especially for heat stability (see Chapter 12). Smallpox was nevertheless eradicated from the country, primarily because of the care exercised by staff in the storage and transportation of vaccine.

Producers in North America supplied large amounts of vaccine of good quality to the global programme. However, during the early stages of the programme there were problems of lower potency with some batches produced in the USA for jet injectors. In 1974, some batches of vaccine from Canada were also found to be of unsatisfactory potency. However, these were very occasional failures and the quality was quickly improved when the deficiencies were drawn to the attention of the producers.

In Africa, vaccine from Guinea and Kenya was of good quality and was used in their national programmes, some also being donated to other African eradication programmes. Production facilities that had been established in Ethiopia, Rwanda and Zaire soon discontinued production because of unsatisfactory results in tests of vaccine samples and an assessment by consultants that the production problems could not be readily overcome. Efforts were made to improve the quality of vaccine produced in the Nigerian laboratory, but these proved unsuccessful.

In the WHO Eastern Mediterranean Region, excellent vaccine was produced in Iran from 1972 onwards and was used both for the national vaccination programme and in Pakistan, through donation to WHO. Samples of good-quality vaccine were also received from the Syrian Arab Republic, beginning in 1973, but no other laboratories in this region were successful in producing satisfactory freeze-dried vaccine.

In South-East Asia, excellent progress was made in 8 production laboratories in 4 countries, the results of testing after 1971 being generally satisfactory.

Samples from the 4 laboratories in the Western Pacific Region which produced vaccine for their own use or for donation were all satisfactory.

All the European producers enumerated in Table 11.13 produced vaccine for donation to WHO, a sample of each batch being sent to the WHO International Reference Centre for confirmation of their own assay results. A few batches from the USSR tested before 1971 failed to meet WHO requirements, as did a few batches sent from Switzerland in 1972. Since the 2 laboratories in question were major suppliers of vaccine to the global smallpox eradication programme, the failure of these batches to meet the requirements was of concern to both WHO and donor governments. Following an intensive review of procedures, the quality of vaccine supplied by both laboratories improved so that WHO requirements were regularly met.

From 1973 onwards there was enough good-quality vaccine, produced locally or donated to WHO, both to cover adequately the needs of endemic countries and to extend the supply to adjacent countries at risk, as well as countries in which maintenance vaccination was continuing.

Experience with this quality control programme provides some useful lessons. First, even sophisticated laboratories in the industrialized countries produced substandard vaccines—albeit infrequently—indicating that all vaccine must be subject to quality control. Secondly, with adequate technical advice, certain laboratories in endemic countries were successful in producing high-quality

1978

Plate 11.9. Anton C. Hekker (b. 1928) was head of the WHO International Reference Centre for Smallpox Vaccine at the National Institute of Public Health, Bilthoven, Netherlands, established in 1967. He provided invaluable help in ensuring effective quality control of vaccine used in the global smallpox eradication programme and in helping manufacturers in endemic countries to produce high-quality vaccine.

vaccine in large quantities. Lastly, quality control contributed to the decision by a number of governments to discontinue production when it became apparent that their vaccine failed to meet WHO standards.

VACCINE PRODUCTION IN ENDEMIC COUNTRIES

In the interests of self-sufficiency, many endemic countries wished to embark on the production of freeze-dried smallpox vaccine. For all or even most to do so would have been uneconomical in scale of production. Thus, it was necessary to develop a policy based on population size, so as to limit the number of countries to which WHO assistance would be provided.

"If a laboratory is suitable for upgrading to enable it to make freeze-dried smallpox vaccine, it should be equipped to produce at least 500 000 containers a year, each containing 0.25 ml of vaccine. This is equivalent to about 125 litres [12.5 million standard doses]. Countries not planning to produce this quantity of vaccine annually would be ill-advised to initiate production." (*Methodology of Freeze-dried Smallpox Vaccine Production*; SE/68.3 Rev.2.)

For example, vaccine production in a country with a population of less than 10 million would be uneconomic, since in such a country only 2 or 3 million doses of vaccine would be required annually, an amount that would ordinarily be produced in 10 or 15 production batches, in a few months. Such a production effort would not justify the necessary investment of manpower, equipment and WHO training resources.

However, local production in the larger endemic countries was of the utmost importance, since such large amounts of vaccine were needed. For example, the combined population of Bangladesh, India and Indonesia in 1972 was estimated to be about 762 million—i.e., roughly half the population of all the countries in which smallpox was endemic in the late 1960s. Both WHO and UNICEF provided substantial assistance to these countries, each of which produced large quantities of vaccine and became self-sufficient (Table 11.14). Indeed, in the later stages of the campaign, India became a vaccine donor (see Table 11.15).

During the mid-1960s, a number of laboratories in Africa produced liquid vaccine and some endeavoured to convert to the production of freeze-dried vaccine, but only a few were successful. WHO provided support to 3—Guinea, Kenya and Nigeria—but only the first 2 were successful in consistently producing satisfactory vaccine. In addition, Mozambique and South Africa produced satisfactory freeze-dried vaccine.

Table 11.14. Smallpox vaccine production in Bangladesh, India, and Indonesia, 1966–1977[a]

Year	Production (thousands of doses)[b]		
	Bangladesh	India	Indonesia
1966	..	21 223	..
1967	..	21 173	..
1968	..	34 675	7 506
1969	..	53 493	20 057
1970	..	42 398	22 149
1971	..	40 291	16 720
1972	8 585	52 853	7 377
1973	20 175	87 898	4 180
1974[c]	24 088	132 112	1 763
1975	18 254	141 364	..
1976	11 469	107 603	..
1977[d]	17 590	84 485	..

[a] Populations in 1972 (millions):
Bangladesh: 70.4
India: 577.4
Indonesia: 126.2
[b] .. = data not recorded.
[c] Indonesia certified smallpox-free.
[d] Bangladesh and India certified smallpox-free.

Of the WHO-supported efforts, that of Kenya was the most successful. The laboratory in Kenya had been producing liquid vaccine for its own use and for sale to other countries in eastern Africa since the 1930s. The Smallpox Eradication unit, thinking that it might be possible to develop regional centres for vaccine production, took Kenya as a possible model. In practice, an unforeseen economic problem arose in developing the laboratory as a regional resource. To encourage the use of freeze-dried vaccine, it was WHO's policy to provide it free of charge to endemic countries. However, Kenya needed to recover the set-up and production costs of vaccine it supplied to other countries. Yet these countries could hardly now be asked to buy freeze-dried vaccine from Kenya when other countries received their vaccine free through WHO.

The problem was solved by supplying Kenya with materials needed to produce all of its freeze-dried vaccine, thus offsetting needed expenditures for additional vaccine production for donation to other African countries. Between 1967 and 1977 some 28

million doses were produced in Kenya, of which over half was donated to WHO.

Because of its small population (4.1 million in 1972), Guinea did not meet the criteria for WHO assistance for vaccine production, but the WHO Regional Office for Africa was persuaded by the government of Guinea to arrange for substantial WHO assistance, in terms of visits by consultants, freeze-driers, vaccine containers and reagents. Some 1.8 million doses produced in Guinea were eventually donated to the Intensified Programme in 1974 and 1975, but to all intents and purposes production ceased in 1971, when the WHO technical officer working with the project left the country after completion of his assignment.

Mozambique, while still an overseas province of Portugal, consistently produced satisfactory freeze-dried vaccine, and South Africa began producing a satisfactory freeze-dried vaccine in 1970.

In the South-East Asia Region, WHO consultants frequently visited the 4 Indian producers (in Belgaum, Hyderabad, Guindy (Madras) and Patwadangar) as well as those in Bangladesh, Burma, Indonesia and Thailand (see Table 11.9). UNICEF joined with WHO in supplying equipment, spare parts and other supplies, and by 1971 all were making vaccine that met WHO requirements.

In western Asia, efforts in Pakistan (then West Pakistan) to develop national vaccine production were not successful and the eradication programme there relied on donated vaccine. After 1972, good-quality vaccine was produced in Iran, which donated 26 million doses to WHO between 1973 and 1979. Enough vaccine for national needs was produced in the Syrian Arab Republic by 1973.

DONATIONS OF VACCINE AND THEIR DISTRIBUTION

A total of 465 million doses of vaccine, worth US$8.5 million, were donated by 27 countries to the Intensified Smallpox Eradication Programme between 1967 and 1984 (Table 11.15). Some 100 million doses remained at the end of the Programme, and are now kept as part of the WHO emergency vaccine reserve for the post-eradication era (see Chapter 28).

The amounts of vaccine distributed annually to 70 countries or organizations between 1967 and 1979 have been given in Chapter 10, Table 10.9. Between 15 and 45 million doses of vaccine were dispatched annually to the endemic countries, in addition to the very substantial quantities that were produced locally or donated through bilateral aid programmes.

The problems of effectively distributing the small amounts of vaccine that were donated to WHO between 1958 and 1966 were resolved by centralizing distribution through the Smallpox Eradication unit, which rented cold-storage space in Geneva. Each country that had pledged donations of vaccine was asked to send such donations to the unit as soon as they were available. Charts assessing current and future vaccine requirements for all countries were drawn up. When a request was received from a country, the

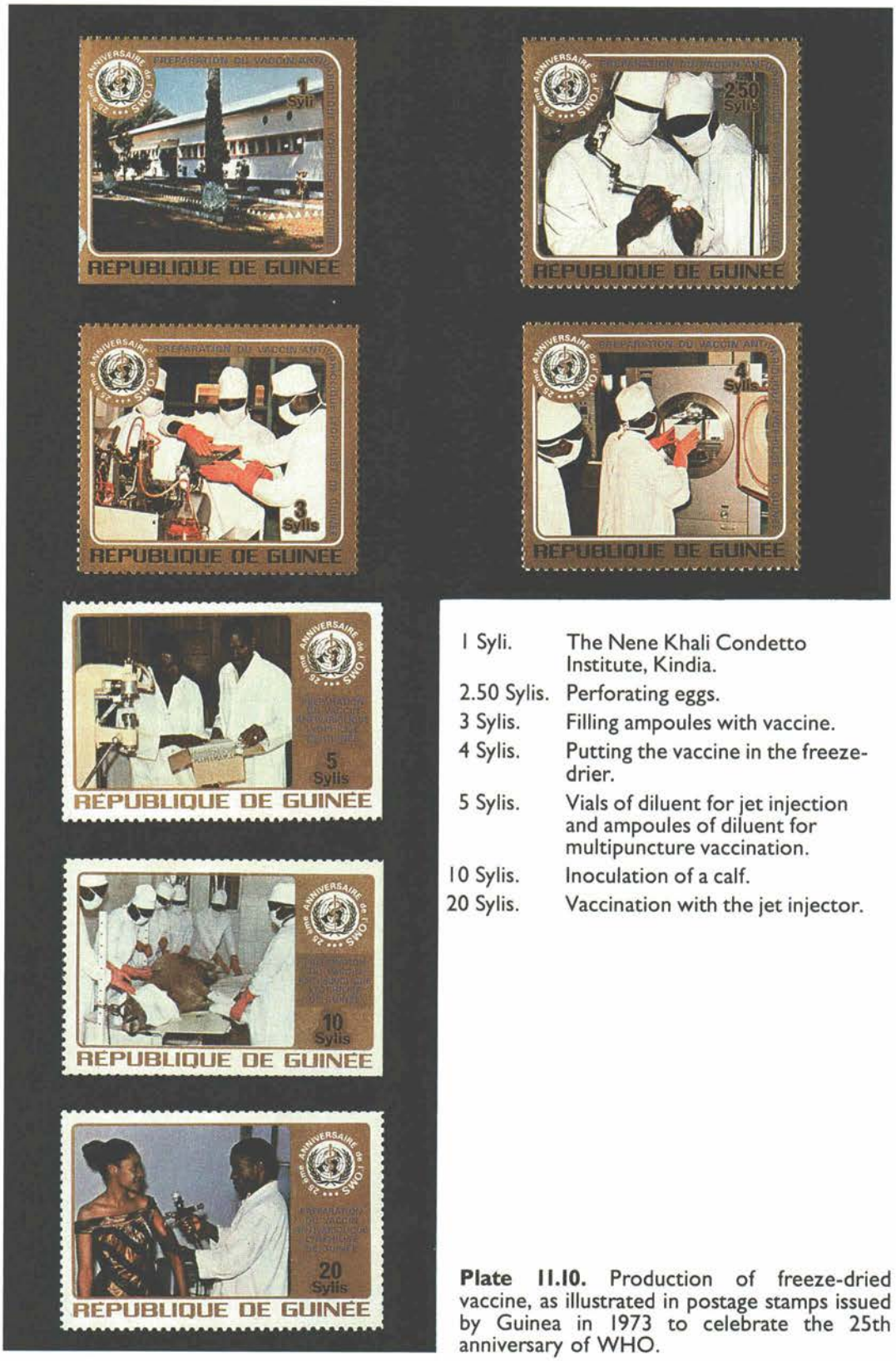
Table 11.15. Smallpox vaccine contributed to the WHO Voluntary Fund for Health Promotion, Special Account for Smallpox Eradication,[a] 1967–1984

Country or area	Number of doses
Argentina	810 000
Belgium	13 840 200
Brazil	7 795 000
Canada	41 448 290
China (Province of Taiwan)	400 000
Colombia	300 250
Czechoslovakia	850 000
Finland	563 650
France	200 000
German Democratic Republic	2 138 000
Guinea	1 825 900
Hungary	2 750 055
India	15 120 000
Iran	26 000 000
Jordan	5 000[b]
Kenya	14 950 000
Monaco	277 500
Netherlands	11 109 025
New Zealand	1 050 000
Peru	300 000
Philippines	250 000
Sweden	1 000 000
Switzerland	18 604 925
Thailand	400 000
USSR	298 146 900
USA	2 418 200
Yugoslavia	2 600 000
Total	465 152 895[c]

[a] Donations made in kind.

[b] Liquid vaccine not used for the eradication programme but shipped to a country in the temperate zone.

[c] 100 million doses of multipuncture vaccine donated by Belgium, the German Democratic Republic, India, Iran, the Netherlands, and the USSR which were not required for the eradication programme are kept in the WHO vaccine reserve in Geneva and Lausanne. Unused vaccine for jet injection has not been retained.



1 Syli.	The Nene Khali Condetto Institute, Kindia.
2.50 Sylis.	Perforating eggs.
3 Sylis.	Filling ampoules with vaccine.
4 Sylis.	Putting the vaccine in the freeze-drier.
5 Sylis.	Vials of diluent for jet injection and ampoules of diluent for multipuncture vaccination.
10 Sylis.	Inoculation of a calf.
20 Sylis.	Vaccination with the jet injector.

Plate 11.10. Production of freeze-dried vaccine, as illustrated in postage stamps issued by Guinea in 1973 to celebrate the 25th anniversary of WHO.

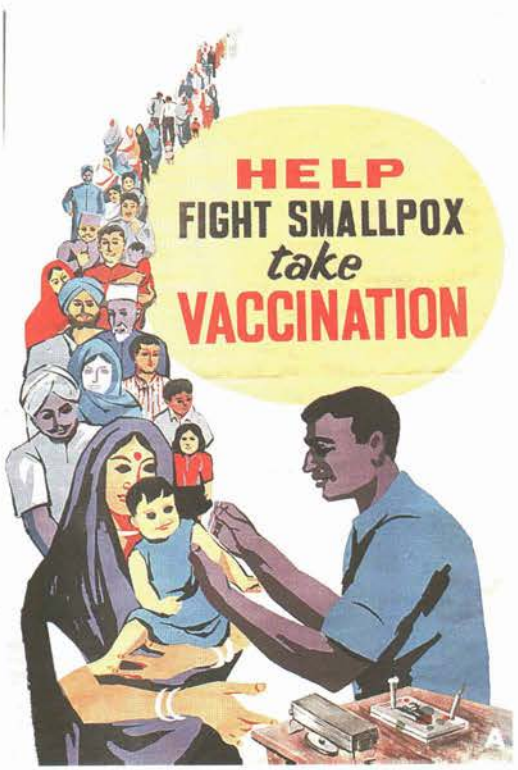


Plate 11.11. Posters promoting vaccination during the Intensified Smallpox Eradication Programme. **A:** India. **B:** Indonesia. **C:** WHO brochure illustrating the technique of vaccination with the bifurcated needle, which was widely distributed.

WHO

Plate 11.12. Vials and ampoules of freeze-dried smallpox vaccine made in Brazil, Canada, Guinea, India, Netherlands, Thailand, USA and USSR, and used in the Intensified Smallpox Eradication Programme.

vaccine required was immediately dispatched by airfreight. During holiday periods, such as Christmas or Easter, special arrangements were made by WHO supply services to ensure that vaccine, if urgently required, could be sent on the earliest possible flight.

Despite these arrangements, the quantity of the vaccine held in stock in Geneva was always small, and often inadequate to meet unexpectedly large demands. It was often possible to send to a country only enough vaccine for 2–3 months' operations, and often donated vaccine was dispatched as soon as it was delivered to Geneva. The situation was especially serious in 1972, when smallpox spread across Iran, Iraq and the Syrian Arab Republic, the demand for vaccine from these countries alone reaching 17 million doses. The situation became acute when the outbreak spread to Yugoslavia, which did not have enough freeze-dried vaccine to deal with the problem. Emergency appeals for donations were made, and the half million doses of vaccine in WHO cold storage were all dispatched to Yugoslavia. Only from 1974 onwards was a sufficient quantity of vaccine able to be held in Geneva.

Most vaccine was dispatched through Geneva, but in some areas it proved practical and more economical to send the vaccine direct from the producer to the recipient country. Thus donations from Kenya were sent direct to other African countries, from Iran direct to Pakistan, and from India direct to Bangladesh, Nepal and Sri Lanka. Several countries in South America assisted each other, as the need arose.

NEW VACCINATION TECHNIQUES

The traditional techniques of vaccination as practised in the early 1960s have been described in Chapter 7. Two new vaccination techniques were introduced in the Intensified Programme: intradermal inoculation by the jet injector in 1967 and multiple puncture inoculation with the bifurcated needle in 1968.

The Bifurcated Needle

Soon after its development and testing, the bifurcated needle (see Plates 11.14 and 11.15) became the standard instrument for vaccina-

tion in the global smallpox eradication programme. Its use simplified vaccination procedures, reduced the quantity of vaccine used and gave a better take rate than earlier vaccination techniques.

History

Liquid vaccine was usually dispensed in sealed capillary tubes containing either one or several doses of vaccine. With single-dose capillaries, the ends were broken and the vaccine applied directly to the inoculation site. With multiple-dose capillaries, the ends were broken and the vaccine was usually put on a plate, from which it was taken up by a glass rod or the vaccination instrument itself and applied to the skin, to be followed by vaccination by scarification (scratch inoculation) or multiple pressure.

When manufacturers produced freeze-dried vaccine in the 1950s, it was packaged in multidose vials or ampoules, in which the vaccine was reconstituted when required by the addition of sterile diluent. A glass rod was dipped into the container and a droplet of the reconstituted vaccine transferred to the surface of the skin, after which vaccination by scarification or multiple pressure was carried out with a lancet or needle. Since this procedure was rather complicated for use in the field, several manufacturers, including Wyeth Laboratories, Philadelphia, the major producers of vaccine in the USA, sought a better method for transferring vaccine from the vial to the skin. Many types of instrument were tested (see box), resulting ultimately in the development of the bifurcated needle, which was found to produce successful results even when used by vaccinators with little training.

Plate 11.13. Benjamin Arnold Rubin (b. 1917) invented the bifurcated needle while working at Wyeth Laboratories, Philadelphia, Pennsylvania, USA.

The bifurcated needle was invented by Dr Benjamin A. Rubin of Wyeth Laboratories, and tested in the field by Dr M. Z. Bierly, who used the conventional multiple pressure method in order to evaluate its efficacy. The needles were patented under United States Patent No. 3 194 237 on 13 July 1965, but Wyeth Laboratories waived all royalties for needles manufactured under contract with WHO.

Use of bifurcated needles in the global smallpox eradication programme

The simplicity of the bifurcated needle as a means of transferring vaccine to the skin and carrying out the vaccination was most attractive but, before recommending its use, WHO organized several studies to ensure that it would be effective in the variety of circumstances met with in various national smallpox eradication programmes. Ladnyi, then a WHO intercountry smallpox adviser in Nairobi, Kenya, Dr H. Mayer, a WHO intercountry smallpox adviser in Monrovia, Liberia, Dr E. Shafa, the regional smallpox adviser in the Eastern Mediterranean Region, and Henderson and Arita from the Smallpox Eradication unit at WHO Headquarters arranged to undertake these studies (SE/72.5). The most important development was the introduction of a new method of vaccination, by multiple puncture rather than multiple pressure.

Vaccination by multiple puncture. Traditionally, vaccine was introduced into the Malpighian layer of the epidermis either by scarification with a needle or lancet or by multiple pressure inoculation with a straight surgical needle (see Chapter 7, Fig. 7.2). Multiple puncture was impossible with a sharp surgical needle because it would penetrate too deeply; moreover, there was a belief that if blood was drawn vaccination was less efficacious. However, the flat prongs of the bifurcated needle prevented too deep an entry into the dermis. Experiments soon showed that the multiple puncture method, in which the bifurcated needle was held at right angles to the skin, which was then punctured several times with the prongs (Plate 11.14), was very efficient and very easy even for an illiterate

Development of the Bifurcated Needle

The bifurcated needle was the result of a developmental study by staff at Wyeth Laboratories but the original idea can be traced back to the early 19th century (D. Baxby, personal communication, 1983). "This operation [vaccination] is usually performed with a common lancet: but one which is fissured by a longitudinal slit, like a writing pen, succeeds rather better" (Moore, 1817).

Of the needle's more recent history, B. A. Rubin (personal communication, 1980) wrote:

"In 1961, I started to test new methods of dispensing the vaccine while also considering the methods of scarification. I collaborated with the Reading Textile Machine Company (now a division of Rockwell International) in needle design. We experimented with various textile needles and filament guides with standard openings as methods for dispensing vaccine. It then occurred to me that a pronged needle would retain the capillary activity of a loop, and that it might have simultaneous utility in scarification. I therefore suggested the use of a sewing needle in which the loop end was ground down to give a pronged fork. A system was devised in which a piece of wire was cut to the right length, and then stamped to give the fork shape, with such dimensions so that the prongs would hold exactly 1 mg of water by capillarity. The machine company then used a mass tumbling system that could sharpen the prongs of the forks of large numbers of needles.

"The sharpened fork was retested and found to hold 1 mg of water quite firmly. When tested with reconstituted lyophilized vaccine, the retained volume tended to be somewhat greater because of the increased viscosity. But the liquid vaccine adhered firmly to the needle. Thus, when the bifurcated tip of the needle is dipped into the vaccine, a constant amount is suspended between the prongs, ready for inoculation."

vaccinator to learn. It became the standard method of vaccination throughout the world.

It was observed that, if certain vaccinators recorded more vaccination failures than expected, it was often because they were too gentle, partly because of the above-mentioned belief that bleeding at the inoculation site reduced the take rate. However, experience showed that this belief was unfounded, and vaccinators were advised to use the multiple puncture method with the bifurcated needle with enough force to cause slight bleeding.

Take rate. Tests carried out in Egypt, Kenya and Liberia (Table 11.16) showed that take rates by the multiple puncture method were in the range of 98–100% in primary vaccinations and that reactions specified as major (see Chapter 7) occurred in 56–82% of revaccinations. In experiments by Dr Shafa in Egypt, in which the same individuals were inoculated on opposite arms by different methods the take rates for revaccination by scarification were slightly lower than those obtained with the bifurcated needle.

Amount of vaccine. The amount of reconstituted vaccine taken up by the bifurcated needle was tested in the Smallpox Eradication unit in Geneva and the results were confirmed in the field. It was estimated that one dip of the needle point lifted an average of 0.0025 ml of reconstituted vaccine between the prongs. Since the amount of reconstituted vaccine used in conventional vaccination was about 0.01 ml, vaccination with the bifurcated needle saved vaccine, permitting 4 times as many vaccinations to be administered with a given quantity of vaccine.

Design of the bifurcated needle. The original needle developed by Wyeth Laboratories was designed to be used once only and then discarded. However, for the global eradication programme it was essential to be able to reuse the needles several times and to make them as cheaply as possible. In collaboration with a metallurgical firm, WHO investigated methods of increasing the carbon content so as to produce the hardest possible steel that would not rust. When this steel was used, metallurgical testing showed that there was no change in the "hardness index" after a bifurcated needle was flamed in a spirit lamp up to 50 times, for 3 seconds on each occasion, but that the index decreased considerably if a needle was flamed for 5 seconds on 25 or more

Plate 11.14. Vaccination with the bifurcated needle. The requisite amount of reconstituted vaccine is held between the prongs of the needle and vaccination done by multiple puncture: 15 strokes, at right angles to the skin over the deltoid muscle, in an area about 5 mm in diameter.

occasions. Furthermore, since the major element in the cost of the needles was the amount of steel contained in each, their length was reduced from 65 mm to 50 mm, and they were made somewhat thinner than the original Wyeth needle.

Durability of needles as modified by WHO. Field tests were carried out on the durability of the smaller, hardened needles. Working in Egypt, Dr Shafa (Table 11.17) observed the frequency of take rates when a single needle was used for 172 successive revaccinations with a vaccine having a titre of $10^{8.6}$ pock-forming units per ml. The needle was flamed before each vaccination by passing it 3 times through the flame of a spirit lamp, and allowed to cool before being dipped into the vaccine vial. Three insertions were performed in each of 172 previously vaccinated individuals; 2 by the scratch method (6–7 mm in length) on one arm, and 1 by multiple puncture (15 strokes within an area 3–5 mm in diameter) on the other arm. The responses were examined on the 6th or 7th day after revaccination. Comparison of the first 86 members of the group with the remainder showed that there were no significant differences in take rates between them but that multiple puncture

Table 11.16. Take rates obtained with the bifurcated needle (multiple puncture) and scratch inoculation

Type of vaccination	Investigator	Country	Vaccination method	Number of subjects observed	Number of major reactions	Take rate (%)
Primary	Ladnyi	Kenya	Multiple puncture	72	71	98.6
	Shafa	Egypt	Multiple puncture	105	105	100
			Linear scratch	105	105	100
	Mayer	Liberia	Linear scratch	30	29	96.7
			Multiple puncture	57	57	100
Revaccination	Ladnyi	Kenya	Multiple puncture	103	58	56.3
	Shafa[a]	Egypt	Multiple puncture	117	88	75.2
			Linear scratch	117	77	65.8
			Multiple puncture	158	121	76.6
			Linear scratch	158	111	70.3
	Mayer	Liberia	Linear scratch	551	396	71.9
			Multiple puncture	49	40	81.6

[a] The same individuals were vaccinated on opposite arms by different methods.

Table 11.17. Comparison of take rates between the first and second half of a series of revaccinations with a single bifurcated needle flamed before each vaccination

Vaccination	First half of group: needle used 1–86 times				Second half of group: needle used 87–172 times			
	Number of vaccinations	Number observed	Number of major reactions	Take rate (%)	Number of vaccinations	Number observed	Number of major reactions	Take rate (%)
First scratch	86	80	43	53.8	86	78	48	61.5
Second scratch	86	80	43	53.8	86	78	53	67.9
Multiple puncture	86	80	58	72.5	86	78	63	80.8

inoculation gave consistently better results than scratch vaccination. Primary vaccinations performed on 93 people, using the same needle, sterilized by boiling, 46 or 47 times, produced takes in all but one person.

Number of puncture sites. The amount of vaccinia virus entering the epidermis could be varied by altering either the number of strokes or the number of insertion sites. Both variations were tested. Dr M. A. Rahman, of the Public Health Institute in Dhaka, Bangladesh (personal communication, 1967), showed that, after the revaccination of individuals who had been vaccinated within the previous 3 years, major reactions were somewhat more common after 30 than after 15 strokes, whereas 5 strokes sufficed to produce takes in the great majority of primary vaccinations.

Possibly as a result of the use of low-titre liquid vaccine, there was a long-standing tradition in many countries that the chance of vaccination failure could be reduced by inoculating in 2 sites, especially in revaccination. During the late 1960s several groups of workers studied this problem. Using vaccine that met WHO standards for potency (10^8 pock-forming units per ml) Pattanayak et al. (1970) showed that there was little advantage in using 2 insertion sites (Table 11.18), and that the bifurcated needle was superior to the rotary lancet for both primary vaccination and revaccination.

Lane et al. (1970a) revaccinated 334 subjects using the multiple puncture method with bifurcated needles, 161 of them at a single vaccination site and 173 matched subjects at 2 sites. There was little difference between the 2 groups in take rates, and no significant difference in titres of neutralizing antibody. On the other hand, Nyerges et al. (1973) found that neutralizing antibody titres were somewhat higher after insertions at 2 sites and suggested that immunity might be more persistent after vaccination in this way.

However, there was general agreement that it was much more important to administer a potent vaccine than to use 2 insertion sites or to increase the number of punctures. With the improvements in freeze-dried vaccine, it was a great deal easier to ensure that the vaccine was potent than to change the method of vaccination. To make the technique in the field as simple as possible, the Smallpox

Use of Bifurcated Needles

WHO procured about 50 million bifurcated needles between 1967 and 1976, of which 5 million are being retained in Geneva together with a smallpox vaccine reserve for emergency purposes (see Chapter 28). The 1970 price of the needles was US$5 per 1000 needles. The other 45 million needles were distributed during the Intensive Smallpox Eradication Programme to practically all the endemic countries in which WHO-assisted smallpox eradication programmes were operating. Additionally, other countries which wanted to strengthen their vaccination programme or had to deal with smallpox epidemics also received the needles. These countries were Democratic Kampuchea, Lao People's Democratic Republic, Malaysia, the Philippines, Sri Lanka and Viet Nam in the Western Pacific and South-East Asia Regions; Bahrain, Iran, Oman and Saudi Arabia in the Eastern Mediterranean Region, and Argentina, Bolivia, Chile, Colombia, Cuba, Mexico, Peru and Venezuela in the Region of the Americas. If the population of the 31 endemic countries in 1967 is included, the total population of countries in which bifurcated needles were used for vaccination programmes would have been about 2000 million.

Eradication unit recommended a single regimen: 15 strokes with a bifurcated needle at 1 site.

Detailed instructions (SE/68.2 Rev.1) were widely circulated and it was pointed out in them that, with the multiple puncture method, a trace of blood indicated that the punctures were likely to have introduced the virus into the epidermis.

Containers for bifurcated needles

The package of smallpox vaccine prepared by Wyeth Laboratories contained freeze-dried vaccine, fluid for reconstitution, and bifurcated needles in a disposable plastic container. Disposable appliances were, however, too expensive to be used in the global smallpox eradication programme, and early in 1968, the Smallpox Eradication unit sought a plastic container which would hold about 100 needles, would be cheap to produce and could be sterilized by boiling. The containers eventually used were designed by Dr Shafa, who was successful in stimulating local producers in Bangladesh and Pakistan to produce the container illustrated in Plate 11.15. After the conical end had been unscrewed, needles were placed in the containers with the prongs towards the base, and were sterilized by placing the closed container in boiling water. The bottom of the container was provided with a few holes so that the water could be drained or shaken off after boiling. In the field, needles could be removed aseptically from the container one at a time through the hole at the apex of the conical lid, and placed in an empty container after use, for sterilization next day. These procedures

Table 11.18. Results of revaccination of 181 schoolchildren in Delhi, using 2 insertion sites and either the rotary lancet or the bifurcated needle[a]

Titre of vaccine (pock-forming units per ml)	Technique	Takes at both sites (%)	Takes at 1 or both sites (%)	Percentage improvement by use of 2 sites
$10^{8.0}$	Rotary lancet	67.7	83.9	24
	Bifurcated needle	93.2	96.6	3.6
$10^{7.7}$	Rotary lancet	64.7	82.4	27
	Bifurcated needle	73.7	86.9	18
$10^{7.0}$	Rotary lancet	33.4	66.7	100
	Bifurcated needle	61.2	80.6	32

[a] Based on Pattanayak et al. (1970).

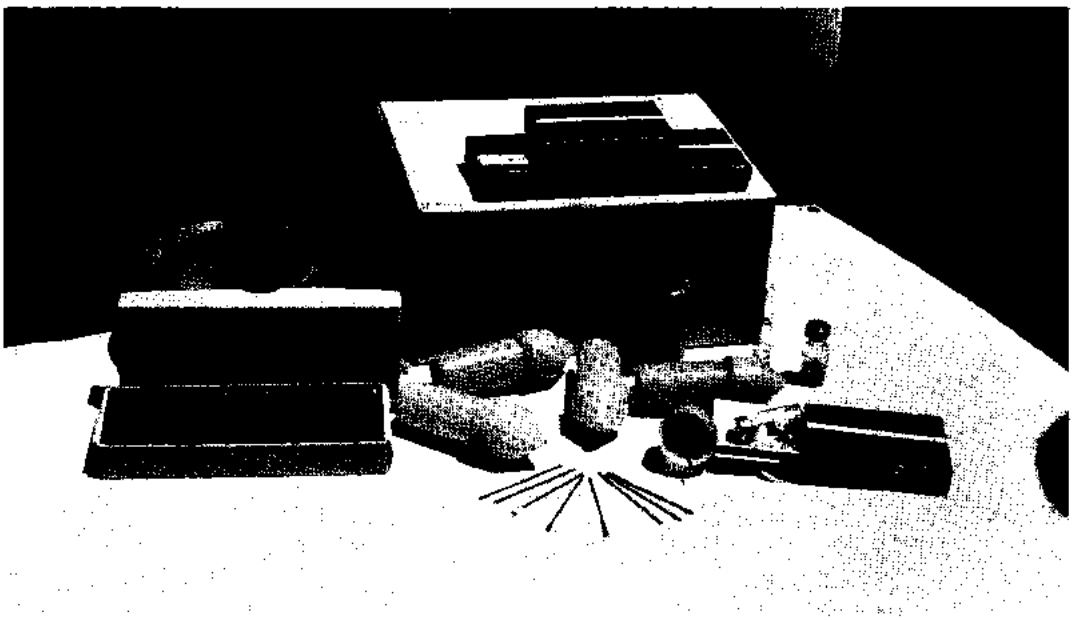


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Plate 11.15. WHO bifurcated needles and plastic containers. The top of one container has been unscrewed so that it can be packed with needles. Holes are provided in the bottom to allow excess water to be removed after sterilization by boiling. Sterile needles are shaken one at a time through the hole in the conical lid.

greatly simplified the vaccinators' work. Subsequently the WHO Regional Office for South-East Asia produced similar containers, and after 1971 they were widely used in all WHO-assisted national smallpox eradication programmes. It is interesting to note that local producers in Bangladesh, India and Pakistan, in which smallpox was endemic, devised a plastic container made of high-density polyethylene which withstood boiling, whereas efforts made by the Smallpox Eradication unit at WHO Headquarters to persuade plastics manufacturers in Switzerland and the USA to produce such containers were unsuccessful.

Packaging and instruction sheets

Initially the packaging and instruction sheets provided with donated vaccine varied, since they followed the regulations of the donor countries. Usually the multiple pressure or scarification method was described, instructions were given about sterilizing the skin and the numerous and complex contraindications to vaccination were listed.

With the introduction of the bifurcated needle, a simple set of instructions in English and French was included in each box of vaccine. In addition, the contraindications to the use of vaccine in endemic countries were simplified in accordance with the policy of the Smallpox Eradication unit, as follows: "In endemic smallpox regions or in areas geographically proximate only individuals who are severely ill are not vaccinated." This contraindication was included to avoid vaccination being blamed if the patient died. Later some countries making donations on a bilateral basis—for example, India—prepared their own instruction sheets along the same lines.

As the programme progressed, manufacturers were encouraged to provide the vaccine and the diluent in separate packages, so that only the vaccine needed to be stored in refrigerated space, something that was always in short supply in developing countries.

Jet Injectors

Jet injectors (trade name Ped-o-Jet) played an important role during the initial phase of the Intensified Smallpox Eradication Programme. They were used to ensure rapid vaccination coverage with satisfactory take rates in national smallpox eradication programmes in Brazil, Zaire, countries in western and central Africa, and to a small extent in several other countries. In all these countries

Instructions for Smallpox Vaccination with Bifurcated Needle Given in each Box of Vaccine

1. Method for vaccination multiple puncture technique.
2. Site of vaccination—outer aspect of upper arm over the insertion of deltoid muscle.
3. Preparation of skin—none. If site is obviously dirty, a cloth moistened with water may be used to wipe the site.
4. Withdrawal of vaccine from ampoule. A sterile bifurcated needle (which must be cool if flamed or completely dry if boiled) is inserted into the ampoule of reconstituted vaccine. On withdrawal, a droplet of vaccine sufficient for vaccination is contained within the fork of the needle.
5. Application of vaccine to the skin. The needle is held at a 90° angle (perpendicular) to the skin [see Plate 11.14]. The wrist of the vaccinator rests against the arm. For both primary vaccination and revaccination, 15 up-and-down (perpendicular) strokes of the needle are rapidly made in the area of about 5 mm in diameter. The strokes should be sufficiently vigorous so that a trace of blood appears at the vaccination site. If a trace of blood does not appear, the strokes have not been sufficiently vigorous and the procedure should be repeated. Although it is desirable not to induce frank bleeding, the proportion of successful takes is not reduced if bleeding does occur.
6. No dressing should be used after vaccination.
7. Sterilization of needle may be done by flaming or boiling.
   (*a*) Flaming—the needle is passed through the flame of a spirit lamp. It should not remain in the flame for more than three seconds. The needle must be allowed to cool completely before inserting into vaccine ampoule.
   (*b*) Boiling—the needle is sterilized by boiling for 20 minutes. Subsequently, the needle must be dried thoroughly to ensure that the fork of the needle does not contain a drop of water when inserted into the vaccine ampoule.
8. Unused, reconstituted freeze-dried vaccine should be discarded at the end of each working day.

bifurcated needles were also used, especially in rural areas and where only small numbers of people required vaccination. In Brazil, the programme was highly organized and there was no shortage of skilled maintenance and repair staff for the jet injectors. In western and central Africa there was a special reason for using the jet injector—namely, the simultaneous programmes of vaccination against smallpox and tuberculosis in Zaire and against smallpox and measles in western Africa. In other areas, in which only smallpox vaccine was being administered, the bifurcated needle, by virtue of its simplicity and advantages in field use, had been universally adopted by 1969 and had replaced jet injectors where these had earlier been used experimentally.

History

In immunization campaigns in developed countries, undertaken to control the diseases of childhood, immunizing antigens other than smallpox vaccine were administered with syringes and needles. At that time, before disposable equipment had been invented, sterilization between vaccinations was time-consuming, but necessary if serum hepatitis was to be avoided. The jet injector overcame this difficulty. It consisted, in essence, of a piston which forced a measured dose of vaccine, under high pressure, through a narrow orifice, thereby achieving subcutaneous inoculation without the need for syringe and needle.

Hingson et al. (1963) had used jet injection to administer local anaesthetics, insulin and various antibiotics since 1947, and after 1954 the procedure had been used on military recruits for the subcutaneous injection of influenzavirus and poliovirus vaccines. By 1962, vaccination against cholera, DPT (diphtheria, pertussis and tetanus), typhoid and yellow fever was being carried out with jet injectors in Central and South America. All

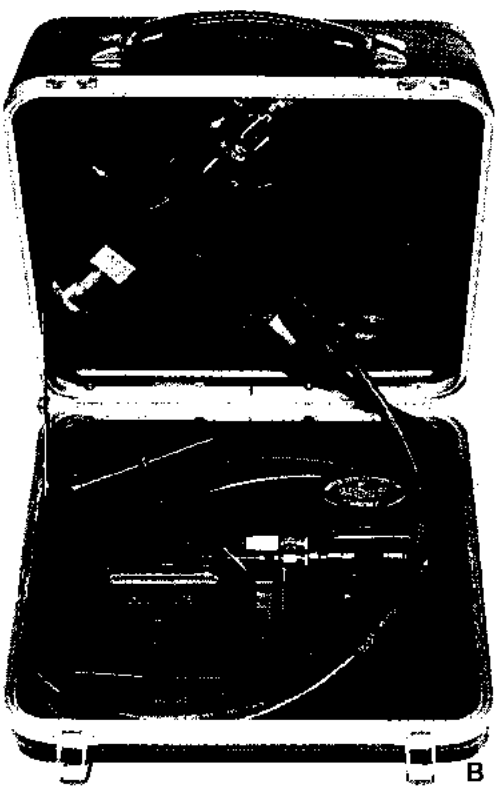

Plate 11.16. The Ped-o-Jet jet injector. **A:** In use in Nigeria. Stepping on the pedal of a hydraulic pump cocked a piston in the "pistol" against a spring and drew in a measured amount of vaccine. The nozzle was placed against the skin and when the trigger was pulled the piston was released forcing a fine high-pressure jet of vaccine into the epidermis. **B:** Assembled in case for transport.

the antigens concerned were introduced subcutaneously by jet pressure, each being given at a different site.

Smallpox vaccination, however, required intradermal deposition of the virus, and in 1962 Dr Aaron Ismach, of the United States Army Research and Development Command, modified the nozzle to enable it to deposit vaccine intradermally (see Millar et al., 1969).

Developmental studies

In July 1962, Henderson and Dr J. D. Millar, using this nozzle attached to a Ped-o-Jet (Plate 11.16), inoculated 41 previously vaccinated young adults with diluted smallpox vaccine; 32 of them showed satisfactory takes (major reactions). These preliminary results prompted a group of scientists in the Communicable Disease Center (CDC—later the Centers for Disease Control) in the USA to conduct a series of developmental studies on the efficacy and safety of intradermal jet injection for smallpox vaccination. Millar et al. (1969) vaccinated 156 volunteers, of whom 16 were unvaccinated and 140 had been vaccinated more than 5 years before, either with undiluted smallpox vaccine by the multiple pressure technique or with 0.1 ml of various dilutions of smallpox vaccine by jet injector, using the newly developed nozzle. Cutaneous and serological responses in revaccinated persons revealed that jet injection of diluted vaccine with a titre of $10^{6.1}$ pock-forming units per ml[1] was as effective as multiple pressure inoculation of undiluted vaccine ($10^{7.6}$ pock-forming units per ml). Among the small number of subjects undergoing primary vaccination, jet injection of diluted vaccine with a titre of only $10^{5.1}$ pock-forming units per ml appeared as effective as multiple pressure inoculation of undiluted vaccine, which suggested that use of the jet injector would result in considerable savings in vaccine. No complications of vaccination, either local (at the inoculation site) or general, occurred in this small series.

Roberto et al. (1969) then conducted studies on cutaneous and serological responses to primary vaccination in 625 children in Jamaica, comparing the jet injection of diluted smallpox vaccine with multiple pressure inoculation of undiluted vaccine. For jet vaccination with diluted vaccine, the take rate depended on the titre as follows:

Titre (pock-forming units per ml)	*Take rate (%)*
$10^{6.1}$, $10^{5.4}$	⩾97
$10^{5.1}$	90
$10^{4.1}$	62

These results can be compared with the take rate of 96% found in persons vaccinated by multiple pressure with undiluted vaccine ($10^{7.6}$ pock-forming units per ml). Subjects who developed Jennerian vesicles usually developed neutralizing antibody (2 failures out of 105 subjects). Seroconversion was not found in those who failed to develop such vesicles. Vesicles and scars were generally smaller in the jet-vaccinated subjects than in those vaccinated by the multiple pressure technique. Vaccinial complications did not occur in any of the 625 subjects, and infants tolerated jet vaccination satisfactorily. Roberto et al. (1969) concluded that intradermal jet injection of 0.1 ml of vaccine with a titre of $10^{5.4}$ pock-forming units per ml or higher was a very effective method of achieving successful primary smallpox vaccination.

These studies showed that intradermal jet injection was satisfactory both for primary vaccination and for the revaccination of individuals who had been vaccinated many years before. Neff et al. (1969) followed up this work with an evaluation of the performance of jet injectors, as compared with the multiple pressure technique, in a well-vaccinated prison population, using serial dilutions of vaccine; they concluded that vaccination by jet injection with a vaccine containing $10^{6.1}$ pock-forming units per ml was at least as efficacious as vaccination by the standard multiple pressure technique.

Freeze-dried vaccine produced by Wyeth Laboratories was employed in all these studies. As used in the field in western Africa, the vials contained a freeze-dried vaccinia virus suspension which was reconstituted with 10 ml of Hanks' solution, so that 0.1 ml, the volume administered by jet injection, contained at least $10^{6.5}$ pock-forming units—

[1] Assays of viral infectivity in this study were carried out by titration in primary rhesus monkey kidney cells using half-log dilution steps, and were expressed as $TCID_{50}$ per ml. Since viral titres elsewhere in this book are expressed as pock-forming units per ml, the published results have been converted from $TCID_{50}$ per ml to pock-forming units per ml, using a factor provided by J.H. Nakano (personal communication, 1982). The tissue culture end-points were about 0.9 log unit higher than the titres on the CA membrane.

considerably more than was required, according to the experimental work.

However, since the improvements in vaccine production procedures, outlined in the earlier part of this chapter, ensured that highly potent vaccine was available, titres in excess of those shown to be necessary in trials were recommended so as to provide a safety margin to allow for the effect of the problems in the handling of vaccine that would inevitably occur in the field at some time or another.

Application

Provided that the instruments could be properly maintained, jet injection, using the special nozzle for intradermal injection, had obvious attractions for mass smallpox vaccination campaigns. In 1965 Millar and his colleagues in CDC undertook a pilot study of jet injection and multiple pressure vaccination in Brazil, the results of which stimulated that country to undertake a national smallpox eradication programme (Millar et al., 1971). They reported that between 27 January and 15 February 1965, 47 926 residents of Amapá Territory, Brazil, living in both urban and rural areas, were vaccinated, all by jet injection. For purposes of comparison, the traditional multiple pressure method was used in Mazagão, where 34 vaccinators, 2 supervisors and 2 local staff vaccinated 911 persons in 3 hours. In Amapá town, in contrast, 2 jet vaccinators, 1 recorder and 2 local staff vaccinated 1335 persons in 6 hours (Table 11.19).

Using data obtained in part of this trial and those collected in a conventional mass vaccination campaign in Belém, Millar et al. (1971) analysed the relative costs of the two methods (see Chapter 12, Table 12.5). Jet injection was found to reduce manpower, transport and vaccine requirements and appeared to be more efficient. In urban campaigns it was estimated that jet injection costs were about one-third of those of conventional techniques. They concluded that jet injection, if intelligently applied, could significantly increase the speed, efficacy and efficiency of national mass smallpox vaccination programmes.

CDC launched a smallpox eradication and measles control programme in 20 countries of western and central Africa in 1967, as part of the WHO global smallpox eradication programme (see Chapter 17). The use of the jet injector was regarded as the key to this programme, since it not only reduced the needs for manpower, transport, the quantity of vaccine and the chances of unsuccessful vaccination but also made possible simultaneous vaccination against smallpox and measles. In 1966, when the Director-General of WHO submitted a report to the Nineteenth World Health Assembly on the organization of the global programme, he specifically referred to the usefulness of intradermal jet

Table 11.19. Comparison of multiple pressure and jet injection vaccination techniques in 2 towns in Amapá Territory, Brazil[a]

Characteristic	Town	
	Mazagão	Amapá
Population	974	1 638
Campaign method	House-to-house visiting	Collecting point and "street sweep"
Inoculation technique	Multiple pressure	Jet injector
Vaccine:[b]		
Titre (pock-forming units per ml)	$10^{8.0}$	$10^{5.8}$
Dose	1 drop	0.1 ml
Amount (tubes)	17	1
Vaccinations:		
Number vaccinated	911	1 335
Number of vaccinators	38	5
Vaccinations per man-hour	8.0	44.5
Percentage of population vaccinated[c]	89.6	78.6
Take rates (%):		
Total	80.8	90.1
Primary	84.6	95.3
Revaccination	76.1	86.7

[a] From Millar et al. (1971).
[b] Egg vaccine was used.
[c] Based on post-campaign survey.

Scars after Vaccination with Jet Injectors

During the Intensified Smallpox Eradication Programme, vaccination scar surveys were often carried out to determine the vaccination coverage of populations. Since the experimental studies with jet vaccination had shown that the resulting lesions and scars were somewhat smaller than those produced by other methods of vaccination, there was some question whether the scars would persist for as long. Dr D. R. Hopkins, of the Communicable Disease Center (CDC) in the USA, studied the persistence of vaccination scars when he was working in Sierra Leone in 1967–1968 and concluded that there was essentially no difference in persistence, whether scars were produced by jet vaccination or by multiple puncture. In 1982, Dr A. Gromyko, while working for the Smallpox Eradication unit, carried out further investigations in Sierra Leone and Côte d'Ivoire and confirmed that, in 80% of subjects, vaccination scars persisted for more than 12 years.

injection for vaccination when large groups could be assembled. WHO provided some 100 jet injectors to the national programmes in Pakistan, the Sudan and Zaire in 1967 and 1968. Some 10 jet injectors were also kept in the Regional Offices for the Eastern Mediterranean, Africa and South-East Asia and in the Smallpox Eradication unit, for emergency use. However, largely because of problems with their maintenance and repair, they were little used except in Brazil, western Africa and Zaire, and briefly in India and Indonesia.

Vaccine for jet injectors

The vaccine to be used in jet injectors had to meet special requirements, relating both to bacteriological sterility and to potency. Because the vaccine was administered parenterally, it was essential that it should have a low to nil bacterial count when tested in the laboratory. This recognized the fact that bacterial sterility could not be achieved unless the vaccine was produced in eggs or tissue culture (see box opposite), and no laboratories at that time produced such a vaccine which met other WHO standards of potency and heat stability. Although the vaccine had inevitably contained a few non-pathogenic bacteria, no unusual complications due to bacterial infection had been observed during the extensive field trials of the jet injector. As a working standard, a WHO Scientific Group on Smallpox Eradication (1968) noted that vaccine containing up to 5 non-pathogenic bacteria per ml had been extensively used for jet injection without untoward effects.

In the smallpox eradication programmes carried out with United States assistance in 20 countries of western and central Africa, freeze-dried calf lymph vaccine produced by Wyeth Laboratories was used. Low or zero bacterial counts per ml were achieved with this vaccine by frequent and meticulous cleansing of the animal skin from the time of inoculation to that of harvest. Producers in Switzerland and the USSR were likewise successful, as were some others, in providing a vaccine of low bacterial content, and this vaccine was used in Zaire. For Brazil, the vaccine was produced in Brazilian laboratories, and although many batches of the vaccine contained more than 5 non-pathogenic bacteria per ml, and sometimes some pathogenic bacteria, no adverse consequences were detected during the eradication programme in Brazil.

The other feature of the vaccine used for jet injection was that the recommended titre of the reconstituted vaccine was lower than that required for multiple pressure vaccination—namely, $10^{6.5}$ instead of $10^{8.0}$ pock-forming units per ml—since all the virus in the injected dose was introduced into the skin, rather than a minute fraction as in the multiple puncture method. Wyeth Laboratories produced a special vaccine vial which, when reconstituted with 50 ml of saline (a quantity sufficient to vaccinate 500 persons), gave this titre. When other vaccines were used, a dilution factor was chosen to give the same final concentration. For example, the vial used for vaccine produced in the USSR contained the freeze-dried residue of 0.2 ml of vaccine with a minimum concentration of vaccinia virus of 10^8 pock-forming units per ml. One ampoule of this vaccine diluted with

Bacterial Counts of Vaccine Used in Jet Injectors

Bacteriologically sterile smallpox vaccine can be produced on the CA membrane or in cultured cells. However, the vast majority of producers used animal skin, and the resulting vaccine always contained some bacteria. The number of viable bacteria could be reduced by treatment with phenol, but it was impossible to produce bacteriologically sterile vaccine which remained potent in terms of its viral content. The term "bacterial count zero" (see Table 11.7) does not mean "bacteriologically sterile" but only that no viable bacteria were found in the samples tested.

A conflict arose in the framing of standards for vaccine for use in jet injectors because of the insistence by experts on biological standardization that all vaccine designated for parenteral use in man should be bacteriologically sterile and the pragmatic view expressed by the WHO Scientific Group on Smallpox Eradication (1968) that freeze-dried vaccine containing up to 5 non-pathogenic bacteria per ml of reconstituted vaccine had been used for jet injectors in recent extensive trials without untoward effects. In fact, no new standards were drawn up by WHO. However, in 1969 the United States health administration proposed that the vaccine for jet injectors should pass the same sterility test as that used for other vaccines for parenteral use (*Federal Register*, 1969). At that time Wyeth Laboratories were supplying the jet injector vaccine, and although the bacterial count was often zero it was not bacteriologically sterile. Hence the concern of Dr J. H. Brown of Wyeth Laboratories, Henderson of WHO, and Dr D. Millar of CDC, all of whom believed that the requirement was academic and would hamper the progress of the eradication campaign in western Africa, sponsored by the USA, where jet injectors were a major tool. Discussions took place with the United States health administration and eventually the requirement was not imposed.

about 6.6 ml of saline therefore gave a final concentration of about $10^{6.5}$ pock-forming units per ml. However, since in practice the vaccine had a virus concentration of 2 or 3 × 10^8 pock-forming units per ml, the vaccine in 2 ampoules was usually diluted with 25 ml of saline (a lot size easily available on the market) for intradermal jet injection. In places in which the Wyeth vaccine and the corresponding diluent were not available, WHO provided national eradication programmes with special vials containing 25 ml of saline together with instructions for dilution. Sometimes, by mistake, distilled water was used to reconstitute the freeze-dried vaccine. Vaccine so reconstituted caused a sharp pain when injected, which was not the case when saline was used as the suspending fluid, but it proved satisfactory otherwise.

Manuals in English, French and Portuguese, describing the maintenance and repair of jet injectors, were developed by the Communicable Disease Center and produced for national vaccination campaigns in which this instrument was used.

Discontinuation of use of jet injectors

A few disadvantages of jet injectors emerged during the campaigns in which they were used. In contrast to the simplicity of bifurcated needles, the jet injector required meticulous care and maintenance and considerable repair skills, which could not always be provided despite all the efforts to prepare a detailed, profusely illustrated manual. Furthermore, the instrument was expensive and heavy. With the introduction of bifurcated needles in 1968, it became apparent that these were far more functional, and in well-organized campaigns it was found that individual vaccinators could vaccinate 1000–1500 persons per day. At the same time, experience with jet injectors showed that vaccinations teams were seldom able to assemble more than 2000–3000 persons per day, on average, hence the jet injectors offered little advantage. Thus their use was largely confined to the programmes begun in 1967–1968—in Brazil, countries of western and central Africa, and Zaire.

Other jet injectors

In 1968 and 1969, Arita coordinated investigations of several other devices developed by various manufacturers: the Press-o-Jet, a hand-operated jet injector produced in the USA, the Dermojet (modified as the Vaccijet) produced in France, and the Porton needleless injector produced in the United Kingdom. Some experimental models were sent to Kenya and their suitability was tested in the field by Ladnyi. None of these instruments proved as satisfactory as the better-established Ped-o-Jet with regard to take rates, mechanical reliability or general convenience. By 1969, the advantages of the bifurcated needle had been fully recognized, and the studies were discontinued.

MODIFICATION TO VACCINATION PROCEDURES

Preparation of Skin

The principal modification to previously used procedures related to the cleansing of the skin prior to vaccination. It was generally believed that bacteria on the surface of the skin might cause infection if introduced during vaccination. For smallpox vaccination it was usual to cleanse the skin with acetone or 70% alcohol. With the latter, such cleansing, to be effective, had to continue for about 15 seconds, although even then there was no assurance that the skin would be free of spore-forming bacteria. However, if vaccine was deposited on the skin before it was completely dry, the potency could be reduced by the residual alcohol.

According to the *Memorandum on Vaccination against Smallpox* (England and Wales, Ministry of Health, 1962), "Many doctors use nothing at all if the arm is reasonably clean, and there is no evidence to condemn this practice". Subsequently, Dann (1966) reported that, when 1078 intradermal, subcutaneous, intramuscular and intravenous injections were done without preparation of the skin, there was no subsequent infection. He concluded that "at best, then, pre-injection skin preparation reduces the risk of infection and probably in practice it has no useful effect whatsoever". The *Handbook for Smallpox Eradication Programmes in Endemic Areas* (SE/67.5 Rev.1) stated that no pretreatment of the skin was necessary for vaccination but that, if the site was obviously dirty, the skin should be wiped with a cloth moistened with water. This minor change from the traditional method greatly facilitated vaccination programmes, since it dispensed with the need for additional material such as cotton swabs and antiseptics and speeded up the operation. It was subsequently discovered that, in the smallpox eradication programme in Iran in 1953–1961, glycerolated lymph had been administered by the scratch method to over 30 million persons in whom the site was not cleansed, since the use of alcohol and even soap was not recommended for fear of inactivating the virus: no serious local infections were reported (WHO/SE/78.120).

Neonatal Vaccination

As has been noted in Chapter 7, in the early 1960s Rao had introduced the practice of neonatal vaccination in hospitals, first in Madras and subsequently throughout urban areas in south India. The WHO Expert Committee on Smallpox (1964) recommended that in endemic areas primary vaccination should be carried out as early as possible, preferably in the neonatal period, and repeated about 12 months later. This view was reinforced in 1967 (WHO Scientific Group on Smallpox Eradication, 1968) and again in 1971 (WHO Expert Committee on Smallpox Eradication, 1972).

During the intensified eradication programme in India, neonatal vaccination was widely practised in municipalities and corporations, where the majority of births occurred in health institutions and maternity centres whose staff were provided with vaccine and bifurcated needles and trained in their use. Similar procedures were adopted in certain African countries, where births occurred in health institutions or were assisted by experienced midwives. However, in the rural areas of the Indian subcontinent and in most parts of Africa, neonatal vaccination was not possible, and efforts were therefore made to vaccinate infants at the first health examination, where such facilities existed.

THE SEARCH FOR NEW VACCINES

As has been mentioned earlier in this chapter, at the outset of the Intensified Smallpox Eradication Programme in 1967 the Smallpox Eradication unit reached the

conclusion that smallpox could be eradicated by the effective use of the vaccine then available. Not only did it see no need for a new vaccine but it also feared that the trials that such a product would have to undergo would act as a brake on the global eradication programme. Since, despite the tremendous amount of work involved in coordinating this programme, the unit at its largest consisted of only 6 professional and 4 supporting staff, extremely careful attention had to be given to the determination of priorities.

However, advanced industrial nations which had eliminated smallpox decades earlier saw the problem from a different perspective. Health officials and the public alike were concerned by the sickness, occasional complications and, rarely, death that followed the administration of existing smallpox vaccines. Virology had advanced a long way since 1798, when vaccination had first been introduced, and many workers, especially in Europe, Japan and the USA, sought a vaccine that would be associated with milder lesions after primary vaccination and especially with less likelihood of complications.

Methods of improving smallpox vaccine, from the point of view of reducing complications, were extensively discussed; first, in 1969, at a symposium on smallpox organized in Zagreb by the Yugoslav Academy of Sciences and Arts, (Gušić, 1969) and again in 1972, when a special session on smallpox vaccination was convened in Bilthoven by the International Association of Biological Standardization (Regamey & Cohen, 1973). Three approaches were adopted in the studies designed to develop less reactogenic vaccines: (1) selection of the least reactogenic strains from among those currently being used for vaccine production; (2) development of an attenuated strain; and (3) use of inactivated vaccine. The second and third approaches included attempts to develop a method in which attenuated or inactivated vaccine was first used to provide an initial immunological stimulus and thus partial protection, followed by vaccination with the usual smallpox vaccine, a procedure which should in theory reduce complications. A fourth series of investigations, largely independent of the issue of vaccinial complications, was aimed at developing a tissue culture vaccine which, unlike vaccine of animal skin origin, would be sterile. None of these attempts resulted in an alternative vaccine which could be widely used for the global smallpox eradication programme. Nevertheless, the efforts of laboratory investigators and epidemiologists in these once important research activities are significant for the historical record. If attempts to immunize human beings against a variety of diseases by the incorporation of designated foreign genes in vaccinia virus are successful, there will be renewed interest in methods of reducing the incidence of severe complications.

Selection of Vaccinia Virus Strains of Low Pathogenicity

Polak et al. (1963) reported on the pathogenicity to man of vaccines made with the Bern, Copenhagen, Ecuador and Lister strains of vaccinia virus. The generalized responses, in terms of the degree of morbidity (the ratio of number of bed-patients to number of successful vaccinations), high fever, and prolonged fever in bed-patients, were recorded. The Lister strain produced the mildest response, followed by the Ecuador strain. The Copenhagen and Bern strains were similar in their effects and of greater pathogenicity than the other two. Thus, when a sound evaluation method was used with adequate controls, it was demonstrated that vaccinia strains differed in their pathogenicity to man. In addition, the study suggested that the potency of the vaccine (in terms of its titre) seemed to have no bearing on the course of illness following vaccination. These results supported the views held by many epidemiologists that different strains of vaccinia virus were associated with different frequencies of complications (see Chapter 7). For example, the Bern strain, once used in Austria, Germany, Switzerland and Yugoslavia, had been associated with much higher complication rates (especially of postvaccinial encephalitis) than those reported in the United Kingdom (in which the Lister strain was used) or the USA (in which the New York City Board of Health strain was used). By 1971, these countries, with the exception of Yugoslavia, had changed to the Lister strain for vaccine production, and from that time on the complication rates decreased.

In the 1960s, Dr Marennikova and her colleagues in Moscow collected vaccinia strains from different vaccine producers and studied their pathogenicity, as determined by inoculation by various routes into rabbits, mice and irradiated rats. Table 11.20 sum-

Vaccinia Virus Strains

It is impossible to review comprehensively the origin and nature of the various vaccinia virus strains which have been used by laboratories since early in this century. Of 35 strains, many of which were used only for laboratory studies and not for vaccination, whose origin had been investigated by Wokatsch (1972), 7 were said to have been derived from variola virus: Dairen (Japan), Ikeda (Japan), Lister (United Kingdom), LMC (United Kingdom), Tashkent (USSR), Temple of Heaven (China) and Williamsport (USA). However, all early experiments on the adaptation of variola virus to growth in calves were done in vaccine production laboratories. Restriction endonuclease analyses of variola and vaccinia DNAs, and the negative results of Herrlich et al. (1963), whose experiments were conducted in premises in which vaccinia virus had never been used, suggest that the so-called transformation of variola virus into vaccinia virus was due to contamination.

Four strains—namely, EM-63, Lister, New York City Board of Health, and Temple of Heaven—were the strains most widely used for vaccination, and have been inoculated into perhaps one-third of the population of the world since 1950. It is of interest to examine their histories.

The *EM-63* strain was widely used in the USSR and between 1967 and 1970 was the strain used for vaccine donated to the WHO Intensified Smallpox Eradication Programme and in many bilateral aid programmes. It was received in Moscow in 1963 from Ecuador via Denmark, where it had been passaged in rabbits and calves. The Ecuador strain was in turn derived in 1940 from the strain used by the Massachusetts Department of Health, Boston, USA (Edsall, 1973), where it had been used for many years for the production of a vaccine with a long history of innocuity. It appears to have originated from the New York City Board of Health strain.

The *Lister* strain was said to have been isolated in the Vaccine Institute in Cologne, Germany, from a Prussian soldier suffering from smallpox in the Franco-Prussian war in 1870. It probably arose as a result of contamination with the Institute's own vaccine strain (Wokatsch, 1972; C. Kaplan, personal communication, 1982). The strain has been used in the United Kingdom since 1892 and at the Lister Institute since 1916. It was passaged through man initially, then rabbit and sheep skin in alternation. It was used in the development of the International Reference Preparation of Smallpox Vaccine established in 1962. After transfer to other laboratories it was also called the Liverpool, Mérieux 37 and Nigeria strains. A derivative of the Lister strain (L-IVP) was used for the production in the USSR after 1971 of most of the vaccine donated to the Intensified Smallpox Eradication Programme.

The *New York City Board of Health* strain appears to have had a somewhat lower pathogenicity, in terms of the frequency of complications, than any other widely used vaccinia strain. According to the American Type Culture Collection, the New York City Department of Health Laboratories started manufacture of smallpox vaccine in 1876 with seed virus supplied by Dr J. Loines, who brought it over from England in 1856. This strain was distributed to many other laboratories, where it acquired different names, such as IHD, LED-O, Noguchi, WR and Wyeth, and different biological properties if it was passaged in different ways, especially if intratesticular or intracerebral injection of rabbits was employed.

The *Temple of Heaven* strain was used for the smallpox eradication programme in China. In 1926, pus from a smallpox patient was passed 3 times in monkeys, then 5 times in rabbits (skin/testes), 3 times in calf skin, 1–2 times in rabbit skin and a further 1–3 times in calf skin. Contamination with vaccinia virus probably occurred during these passages.

Table 11.20. Classification of strains by degree of pathogenicity[a]

Country of origin	Strain
High pathogenicity	
China	Temple of Heaven
Denmark	Copenhagen
France	Paris
Hungary	Budapest
Japan	Dairen, Ikeda
USSR	Gam, MRIVP, Per, Tashkent, TBK, Tom
Moderate pathogenicity	
Federal Republic of Germany	Bern
India	Patwadangar
USSR	BIEM, B-15
United Kingdom	Lister
Low pathogenicity	
USSR	EM-63
USA	New York City Board of Health

[a] Based on Marennikova et al. (1969).

marizes the results obtained for a number of different strains (Marennikova et al., 1969). Subsequent investigations (Marennikova, 1973) showed that the Tashkent strain was associated with much higher levels of reported postvaccinial complications (46 cases per million doses distributed, with 18 per million of encephalitis) than the B-51 or especially the EM-63 strain (17 per million doses with 7 per million cases of encephalitis for EM-63). Likewise, the Wyeth (New York City Board of Health) strain, of low pathogenicity for experimental animals, was associated with a relatively low rate of postvaccinial complications (see Chapter 7).

This work, which was presented at two major conferences of vaccine producers, influenced health authorities' decisions as to the choice of a strain, particularly as additional epidemiological data became available. For example, the Tashkent strain, which according to Dr Marennikova was highly pathogenic for animals, had been used in the USSR for the production of smallpox vaccine for local use and for donation to India and other Asian countries up to 1966. It caused considerable concern among Indian health workers because of the severe local reactions (Goyal et al., 1969), and after 1966 its production was discontinued in the USSR.

Table 11.21, based on data from WHO surveys in 1968 and 1971, shows how vaccine producers in several countries changed from the strains they had previously been using to the less reactogenic Lister strain, which was distributed by the WHO International Reference Centre both as a reference vaccine for potency assays and as seed lots for vaccine production. Of 71 vaccine producers in 49 countries or areas, 42 (59%) were using the Lister strain in 1971 compared with 22 (31%) in 1968.

In Japan, complications of smallpox vaccination caused substantial public concern in the early 1970s and the health authorities reevaluated their traditional Ikeda vaccinia strain in comparison with the Lister strain. Country-wide studies of vaccinial reactions, such as fever, the size of lesions, and the need for hospitalization, showed that the Lister strain was less reactogenic, and all 6 Japanese production laboratories changed to it in 1971.

Attenuated Strains

In 1931, Dr T. M. Rivers of the Rockefeller Institute of Medical Research, New York, initiated a series of passages of the New York City Board of Health strain of vaccinia virus through minced chick embryo cells, primarily in order to obtain a bacteria-free vaccine (Rivers, 1931). Passage in rabbit testes was included, initially to obtain a bacteria-free preparation for passage in tissue culture and later to restore the pathogenicity of the virus for rabbit skin. In the process, the virulence of the virus became attenuated.

Two strains were used in subsequent studies; their passage history has been summarized by Barker (1969). Strain CVI-78 had been passed 124 times in chick embryo explants and 19 times on the CA membrane; strain CVII had been carried for a total of 235 passages in chick embryo explants. Rivers & Ward (1935) showed that CVII was suitable for human vaccination by intradermal inoculation. Noting that this tissue culture vaccine consistently produced less severe reactions in rabbits and humans than did the New York City Board of Health calf lymph vaccine, Rivers et al. (1939) carried out further tests, which showed that primary vaccination by intradermal injection of the high-passage tissue culture virus produced only red papular lesions; pustules did not develop and there were few constitutional symptoms. However, they believed that such vaccination would not give complete protection against smallpox, and they recommended that revaccination with the calf lymph vaccine should be carried out 6 months to 1 year later to produce solid and lasting immunity.

Table 11.21. Strains of vaccinia virus used for production of freeze-dried vaccine in 1968 and in 1971[a]

Continent	Country or area	Number of laboratories	Strain used in:	
			1968	1971
Africa	Algeria	1	?	Lister
	Egypt	1	?	Lister
	Guinea	1	Lister	Lister
	Kenya	1	Lister	Lister
	Mozambique	1	Bordeaux	Bordeaux
	Nigeria	1	Lister	Lister
	South Africa	1	?	Lister
	Tunisia	1	Paris	Lister
Americas	Argentina	1	Massachusetts 999	Lister
	Brazil	1	Paris	New York
		1	New York	New York
		1	New York	Lister
		1	Lister	Lister
	Canada	1	New York	New York
	Chile	1	Lister	Lister
	Colombia	1	Lister	Lister
	Ecuador	1	?	Lister
	Peru	1	?	Lister
	USA	2	New York	New York
Asia and Oceania	Burma	1	Lister	Lister
	China	1	Temple of Heaven	Temple of Heaven
	China (Province of Taiwan)	1	Lister	Lister
	Democratic Kampuchea	1	Lister	Lister
	India	1	Lister	Patwadangar
		3	Patwadangar	Patwadangar
	Indonesia	1	Lister	Lister
	Iran	1	Paris	Lister
	Iraq	1	Lister	Lister
	Japan	6	Ikeda	Lister
	New Zealand	1	Lister	Lister
	Pakistan	1	?	Lister
	Philippines	1	Lister	Lister
	Syrian Arab Republic	1	Paris	Lister
	Thailand	1	Lister	Lister
	Viet Nam	1	?	Lister
Europe	Austria	1	Bern	Lister
	Belgium	1	Lister	Lister
	Bulgaria	1	? from Vienna	? from Vienna
	Czechoslovakia	1	Bohemia	Bohemia
	Finland	1	Finland	Finland
	France	2	Paris	Paris
		1	Lister	Lister
	Germany, Federal Republic of	1	Lister	Lister
		1	Hamburg	Hamburg
		1	Bern	Lister
	Hungary	1	Budapest	Lister
	Italy	1	Lister	Lister
		1	?	Lister
		1	Aosta	Aosta
	Netherlands	1	Lister	Lister
	Portugal	1	Bordeaux	Bordeaux
	Spain	1	Spain	Lister
	Sweden	1	Sweden	Lister
	Switzerland	1	Lister	Lister
	Turkey	1	Paris	Paris
	USSR	2	B-51	B-51
		1	Tashkent	LE-IVP (Lister)
		1	Tashkent	EM-63
		1	EM-63	LE-IVP (Lister)
	United Kingdom	1	Lister	Lister
	Yugoslavia	1	Bern	Bern
Total	49	71	19 + 9 unknown	13 + 1 unknown

[a] Based on data from WHO surveys.

The Rivers strains attracted the attention of Dr C. H. Kempe, of the University of Colorado Medical Center, Denver, USA, who was interested in the use of a less reactogenic vaccine in order to reduce the severity of reactions in children suffering from eczema or with other contraindications to vaccination. Using CVI-78, Kempe et al. (1968) vaccinated 1009 patients suffering from eczema (879 primary vaccinations; 130 revaccinations), 326 by the multiple pressure method and the rest by subcutaneous inoculation of graded doses. Local reactions and temperature elevations were much milder than those seen in children vaccinated with standard vaccine and, except for 2 cases of mild erythema multiforme, no patients suffered from virus dissemination or other complications. The mean neutralizing antibody titre of 162 subjects given primary vaccination with CVI-78 by multiple pressure was very similar to that obtained in 45 controls vaccinated with calf lymph vaccine.

Vaccine produced on the CA membrane from the CVII strain of Rivers was used over a period of 5 years for the primary vaccination of more than 60 000 army recruits in the Netherlands to evaluate whether such a strain would reduce complications, as compared with the conventional calf lymph vaccine, which at that time was produced with the Lister strain (Noordaa et al., 1967). All of the recruits received, in addition, 2 ml of vaccinia-immune globulin. The local reaction after primary vaccination with the CVII strain was milder than that with other vaccines and there was only 1 mild case of postvaccinial encephalitis in the 60 000 vaccinations, but the neutralizing antibody titres measured a year after vaccination were also somewhat lower than usual. The research workers in the Netherlands concluded that the use of the CVII strain would probably reduce complications, but that, to produce sufficient protection against smallpox, it should be followed by revaccination with standard calf lymph vaccine 12 months later.

Tint (1973) summarized experience with primary vaccination with the CVI-78 strain in 9000 subjects (3500 of whom had eczema or other skin diseases) in England, Japan and the USA. He suggested that vaccination with this attenuated strain on its own was probably not sufficient to provide protection against smallpox, but that its use in eczematous children as a preliminary to vaccination with standard vaccine would substantially lower the risks of eczema vaccinatum. Such a regimen might be feasible in industrialized countries, but clearly a two-step schedule was out of the question for vaccination in the global smallpox eradication programme.

Because of increasing concern about the morbidity and mortality associated with smallpox vaccination, the National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA, sponsored a study of the reactogenicity and immunogenicity of 4 vaccines: calf lymph and egg vaccine made from the New York City Board of Health strain, egg vaccine made from CVI-78, and Lister sheep vaccine, administered at several dosages by percutaneous and subcutaneous routes (Galasso, 1970). The results were published in 1977 in 6 papers in the *Journal of infectious diseases*. Primary vaccination by the subcutaneous route, while accompanied by lower rates of fever, led to unsatisfactorily low antibody responses both initially and after standard percutaneous revaccination (Galasso et al., 1977). In a comparison of the 4 vaccines, it was concluded that:

"For percutaneous primary vaccination the CV-I strain was 10-fold less infectious than the other three vaccines. CV-I also differed from the other three vaccines in that it produced smaller skin lesions and vaccination was not associated with a febrile response. Only 30% of recipients of primary percutaneous CV-I vaccination with primary type skin responses developed neutralizing antibody; in contrast neutralizing antibody occurred in 82%–85% of the recipients of the other three vaccines.

"After standard challenge vaccination, those children with previous successful percutaneous CV-I vaccination were more likely to have a primary-type skin response. CV-I vaccinees also tended to have larger skin lesions after revaccination, but fever and minor complications were not more frequent. One month after revaccination, neutralizing antibody was present in 93%–96% of those with "takes" on primary vaccination with NYC-CL, NYC-CAM, or Lister vaccines, in contrast to only 75% in CV-I vaccinees."

Thus the Rivers attenuated strains, which had been studied most extensively (Galasso et al., 1977), appeared to be insufficiently immunogenic for use in vaccination against smallpox.

Workers in several other countries developed attenuated vaccines during the 1970s, since it was believed at that time that smallpox vaccination would have to be maintained for many years after eradication and

that an attenuated vaccine would then be necessary. In the Federal Republic of Germany, Stickl and his collaborators (Hochstein-Mintzel et al., 1975) produced a highly attenuated strain of vaccinia virus (MVA) by 572 serial passages of the Ankara strain in chick embryo fibroblasts. In the process, the molecular weight of the viral DNA was diminished by 9% and the strain was shown to have greatly reduced virulence for the chick embryo, laboratory animals and man (Mayr et al., 1978), but its immunogenicity was never adequately tested. Stickl et al. (1974) proposed that it should be used: (1) routinely as pre-immunization for primary vaccinations, when it should be followed by conventional vaccine; and (2) for both primary vaccination and revaccination of all individuals at special risk (e.g., with eczema or under immunosuppression). Its probable safety in immunosuppressed individuals was suggested by experiments in irradiated rabbits reported by Werner et al. (1980).

In Japan, Tagaya et al. (1961) recovered an attenuated strain (DIs) from the standard Japanese vaccine strain Dairen by passage in 1-day-old chick embryos. It produced very small pocks on the CA membrane and was not pathogenic for mice, guinea-pigs or rabbits, but produced small skin lesions and induced antibody production after scarification of the skin of cynomolgus monkeys. The immunity produced in rabbits was poor but antibody levels in monkeys were similar to those produced by the parent strain (Kitamura et al., 1967). Tagaya et al. (1973) concluded that DIs was not suitable for use as a smallpox vaccine, but it might have a role if "prevaccination" became an accepted practice.

Stimulated by Tagaya's results, Hashizume (1975) deliberately sought attenuated variants of the Lister strain by serial passage in rabbit kidney cells at 30 °C and subsequent selection of a small pock from the CA membrane. The variant most extensively studied, LC16m8, was much less pathogenic after intracerebral inoculation in monkeys than CVI, EM-63, Lister or the New York City Board of Health strains (Hashizume et al., 1973), but produced a satisfactory immune response (haemagglutinin-inhibiting and neutralizing antibody) in humans as well as in vaccinated animals (Hashizume, 1975).

In 1974 the Smallpox Vaccine Committee, Ministry of Health, Tokyo, organized a large-scale field evaluation of a number of vaccines, including one produced in rabbit kidney cells with the LC16m8 strain, more than 40 000 persons being vaccinated (Japan, Ministry of Health, 1975). There were no notifiable severe complications among these subjects, those receiving LC16m8 vaccine being closely followed. While the take rates with the LC16m8 vaccine were not significantly different from those of the other vaccines tested, the fewest general responses and smallest local responses were obtained with this vaccine (Table 11.22). Among those receiving LC16m8 vaccine, 1 case of eczema vaccinatum, 3 cases of convulsions and 8 cases of generalized vaccinia were discovered, all of which were mild. It was not clear whether the 3 cases of convulsions were related to the vaccine. The examination of 142 vaccinated subjects by electroencephalography showed that the number of temporary anomalies was lowest in those vaccinated with the LC16m8 vaccine (Table 11.23).

Tests for immunogenicity were carried out in 138 persons vaccinated with LC16m8 vaccine by challenging them with Lister vaccine 12 months later. Major reactions were seen in 18.8%, a rate similar to that observed in 714 persons vaccinated with the Ikeda strain, and challenged with that strain a year

Table 11.22. Results of large-scale study (Japan, 1974) of response to various vaccines[a]

Strain	Year of investigation	Number of subjects	Take rate (%)	Average diameter of induration (mm)	Proportion with fever (>37.5 °C) (%)
LC16m8	1973–1974	10 578	95.1	6.1	7.7
Ikeda[b]	1968–1970	1 506	99.1	18.2	25.0
EM63	1969–1970	1 846	[c]	17.4	21.3
Lister	1968–1971	3 662	93.7	15.3	26.6
CVI	1971–1973	22 976	92.4	16.8	8.5

[a] Source: Japan, Ministry of Health (1975).
[b] Traditional strain used for vaccine production in Japan.
[c] Not available.

Table 11.23. Study of response to various vaccines (Japan, 1974): temporary anomalies on encephalography[a]

Vaccine	Number examined	Number of temporary anomalies on encephalography
LC16m8	56	0
Lister strain	19	5
Lister strain with gamma-globulin	18	1
CVI	30	1
CVI with gamma-globulin	19	0
Total	142	7

[a] Source: Japan, Ministry of Health (1975).

later. Thus it appeared that the immunogenicity of the LC16m8 vaccine was similar to that of other vaccines. Although no field experience was available to provide evidence of the protective effect of this vaccine against smallpox, freeze-dried LC16m8 strain virus grown in rabbit kidney cells is being held as part of a reserve stock of vaccine in Japan. Because of its low reactogenicity and because it can be produced in tissue culture, the LC16m8 strain might be a good candidate for use as a vector for other antigens should this procedure become a practical proposition. The average loss of titre of this vaccine after 4 weeks at 37 °C was estimated to be about $10^{0.4}$ pock-forming units per ml, which is comparable to that of calf lymph vaccine of acceptable heat stability (T. Kitamura, personal communication, 1984).

In 1970 workers in China produced an attenuated variant (G-9) of the Temple of Heaven strain by inoculating children with plaque-purified material and selecting from among those reacting with small skin lesions. The strain produced smaller pocks than the parental strain on the CA membrane and has been used experimentally for the primary vaccination of several million children, but no reports on its immunogenicity or of complications following its use are available.

Inactivated Vaccines

Prior to 1960 only a few live vaccines were available—namely, those for smallpox, tuberculosis and yellow fever—whereas many vaccines consisted of inactivated antigens—pertussis, typhoid, cholera, diphtheria toxoid, tetanus toxoid, etc. Although there are theoretical reasons, discussed in Chapter 3, why inactivated vaccinia virus vaccines, without a follow-up with live virus vaccine, are unlikely to be effective, several research workers undertook developmental studies of inactivated smallpox vaccine in the hope that it might reduce the complications of vaccination.

The earliest study was that reported by Janson (1891), who found that subcutaneous injections of heat-killed vaccine gave equivocal results in children. Many other methods of inactivation were employed (Kaplan, 1962, 1969; Turner et al., 1970) including the use of formaldehyde, ultraviolet irradiation and photodynamic inactivation. Although some of the resulting inactivated vaccines produced neutralizing antibodies in rabbits, none was satisfactory for the primary vaccination of human subjects.

Because complications, especially postvaccinial encephalitis, were very much less common after revaccination than after primary vaccination, several attempts were made to "pre-immunize" subjects with inactivated virus, before inoculation with standard vaccine 1–2 weeks later. Herrlich (1959, 1964) prepared an inactivated vaccine by treatment with formaldehyde, which was used on a small scale in the Federal Republic of Germany and in the German Democratic Republic from the late 1950s as a form of pre-immunization designed to reduce the risk of vaccinial complications. The procedure was to use inactivated "vaccinia-antigen" first and then, 2–3 weeks later, to give conventional live virus vaccine as a booster. In some cases in which pre-immunization was used, the second vaccination produced a large swollen area of erythema and induration surrounding the site of inoculation. In any case, the procedure did not completely eliminate complications. "Vaccinia-antigen" plus vaccinia-immune gamma-globulin, but without follow-up live virus vaccine, was given to 2 elderly patients involved in the Meschede outbreak of smallpox (see Chapter 4) 10–14 days before their exposure, but did not protect either from smallpox, from which one of them died (Wehrle et al., 1970).

A two-step procedure, using gamma-irradiated vaccine for the priming dose, was carried out in a field trial in eastern Europe in 1977 (Marennikova et al., 1978c). One case of postvaccinial encephalitis occurred in a child with congenital macrocephaly, among some

23 000 vaccinated subjects, all of whom were over 3 years of age (S. S. Marennikova, personal communication, 1985).

Production of Vaccine in Eggs and Tissue Culture

Vaccine production on the CA membrane

Soon after the demonstration by Goodpasture et al. (1932) that vaccinia virus would grow on the CA membrane, Goodpasture & Buddingh (1935) published a detailed analysis of the suitability of eggs for the large-scale production of vaccine. The advantages were that production methods were relatively simple and that bacteriologically sterile vaccine could be obtained. Glycerolated egg vaccines were in use in the state of Texas, USA, from 1948 (Cook et al., 1953) and in New Zealand and Sweden from the 1960s.

Freeze-dried vaccine derived from the CA membrane was produced on an experimental scale by Jackson et al. (1956) and on a commercial scale in Sweden (Hedström, 1970). Freeze-dried vaccine prepared on the CA membrane largely replaced calf skin vaccine in Brazil in 1958 (Clausell, 1963) and was used on a very large scale throughout the smallpox eradication programme in Brazil (Voegeli, 1973). Unfortunately, many batches of the Brazilian vaccine did not meet WHO standards for heat stability (see Chapter 12).

Although there has been no evidence of complications or adverse effects caused by avian leukosis viruses in the millions of subjects vaccinated against yellow fever with virus grown in eggs, these agents became a matter for concern when, in about 1967, it was discovered that they were commonly present in eggs. Early in 1970 Swedish producers changed to eggs from flocks free from avian leukosis for smallpox vaccine production.

Vaccine production in cultured cells

As has already been described in relation to the development of the CVI and CVII strains of attenuated vaccinia virus, production in cultured cells began even earlier than in eggs (Rivers, 1931). Over the next 3 decades efforts were made periodically to produce vaccine in cultured cells, at first from chick embryos and later in cell monolayers derived from a variety of sources. However, as with egg vaccine, tissue culture vaccine was not widely adopted, mainly because production in animal skin was simple and cheap and yielded a vaccine that was heat-stable when freeze-dried and was known to protect against smallpox. Furthermore, the seed lot virus system had not been well established when cultured cells first became available for the commercial production of smallpox vaccine,

Avian Leukosis and Egg Vaccine

The WHO requirement for smallpox vaccine from chick embryos (revised in 1965; WHO Expert Group on Requirements for Biological Substances, 1966) indicated that "only eggs from flocks known to be free from disease, including avian leukosis, shall be used". In 1967 a Swedish laboratory proposed to donate egg vaccine to WHO. The vaccine was sterile and thus suitable for jet injector use, but it was produced from flocks which had not been tested for avian leukosis, whose pathogenicity for man was then unknown. In Sweden, egg vaccine had been used for a long time, and Espmark (1969) reported that there had been no increase in leukaemia in the population. Yellow fever vaccine was also being produced in eggs from untested flocks. Despite arguments advanced by Dr Holger Lundbeck, Director of the National Bacteriological Laboratory, Sweden, and by Henderson, the Chief of the Biological Standardization unit of WHO did not agree to accept the donation from Sweden. The Swedish laboratory finally produced a vaccine from leukosis-free flocks and donated vaccine to WHO. However, in Brazil, smallpox vaccine from eggs produced from flocks which had not been tested for avian leukosis, but were almost certainly carriers of the virus, was used throughout the eradication programme, with no known ill effects.

and it was feared that serial passage of vaccinia virus in tissue culture might lead to its attenuation. After 1967, when the Intensified Smallpox Eradication Programme was initiated, WHO did not promote the production of vaccine in cultured cells because it was realized that the success of the eradication campaign was heavily dependent on the production of large amounts of vaccine in laboratories in developing countries, which were unlikely at that time to be able successfully to produce tissue culture vaccine.

In the late 1960s, the WHO International Reference Centre for Smallpox Vaccine initiated a development study with Lister vaccine grown in primary rabbit kidney cells. At the time this was the only tissue culture vaccine comparable with conventional calf lymph vaccine in terms of heat stability, immunogenicity and reactogenicity (Hekker et al., 1973a). The production method was simple and cheap, the vaccine was sterile and free from mycoplasmas and other adventitious agents, and it maintained its potency for up to 8 weeks at 37 °C. The actual reductions in titre, ranging from $10^{0.2}$ to $10^{0.4}$ pock-forming units per ml after 8 weeks at 37 °C, were smaller than those of the calf lymph vaccine tested as a control. The immunogenicity of this vaccine was tested by measuring the neutralizing antibody titres in subjects 1 year after primary vaccination, a control group having been vaccinated with conventional calf lymph vaccine. All the subjects produced neutralizing antibody and there was no significant difference in the results obtained, as between tissue culture and calf lymph vaccines. (Hekker et al., 1973b). Measurement of the antibody titre 2 months after revaccination with the tissue culture vaccine showed an adequate booster effect compared with the calf lymph control group.

Because of these successful results, a field trial on a large scale in Lombok, Indonesia, was jointly organized in 1973 by the Smallpox Eradication unit, the WHO Regional Office for South-East Asia and the government of Indonesia. A total of 45 443 children under the age of 15 years were vaccinated with tissue culture vaccine and the results compared with those for 9061 children of a similar age and sex distribution who had been vaccinated with the standard Lister strain calf lymph vaccine (Hekker et al., 1976). The success rate with tissue culture vaccine reached 97% in primary vaccination and 75% in revaccination (Table 11.24), results comparable with those obtained with the calf lymph vaccine.

The children were carefully followed up for vaccination complications. The only suspected complication was a fatal case of possible encephalitis in a 5-month-old girl who had been vaccinated with tissue culture vaccine, but in Lombok there were many other possible causes of this disease.

Both this tissue culture vaccine and the LC16m8 strain of Hashizume, which was also produced in primary rabbit kidney cells, met the WHO requirements for safety, potency and stability, and were comparable to calf lymph vaccine in effectiveness for both primary vaccination and revaccination. These 2 strains are the only tissue culture vaccines which have been thoroughly and systematically investigated in the laboratory and also to a limited extent in the field. In the Netherlands, the Lister tissue culture vaccine is kept as the vaccine stock for emergency use, both locally and for supply to other countries; the

Table 11.24. Take rates following primary vaccination and revaccination with tissue culture and calf lymph vaccines (Lombok, Indonesia, 1973)[a]

Age group (years)	Primary vaccination				Revaccination			
	Tissue culture vaccine		Calf lymph vaccine		Tissue culture vaccine		Calf lymph vaccine	
	Number	Take rate (%)	Number	Take rate (%)	Number	Take rate (%)	Number	Take rate (%)
≤1	3 894	96.8	695	96.4	189	73.0	43	60.5
1–4	9 136	97.8	1 779	98.0	13 410	78.6	2 693	75.8
5–6	1 108	96.6	229	93.5	8 090	77.4	1 648	74.9
7–14	539	88.1	93	88.2	9 077	65.8	1 881	61.7
Total	14 677	97.1	2 796	96.9	30 766	74.7	6 265	71.2

[a] From Hekker et al. (1976).

LC16m8 vaccine is kept in Japan as a local reserve stock. Either of these vaccines should be suitable for use in the future, should the need arise, when production methods using animal skin are unlikely to be acceptable.

Silicone Ointment Vaccine

Trials were carried out with freeze-dried vaccine suspended in an ointment, so that it could be squeezed on to the skin in the same way as toothpaste from a tube. An ointment vaccine produced by mixing liquid vaccine lymph with lanoline had been produced at the Lister Institute and in Nigeria in the 1960s, but was no more stable than liquid vaccine. In the early 1970s, the Vaccine and Serum Institute, Berne, Switzerland, developed a similar vaccine, in which freeze-dried vaccinia virus was mixed with silicone ointment. The Smallpox Eradication unit recognized the potential value of such preparations for field use and undertook a development study together with the producer and the WHO reference centres. The titration of this preparation presented a problem, since the vaccine was not readily dispersed. After this difficulty had been solved, the WHO International Reference Centre for Smallpox Vaccine discovered that the heat stability was less than that of the standard freeze-dried vaccine. The manufacturers tried unsuccessfully to improve the stability, and the vaccine was never used in the global smallpox eradication programme.

EFFICACY OF VACCINATION

The most persuasive evidence that vaccination was effective in preventing smallpox was the progressive decrease in the incidence of the disease that followed its introduction at the beginning of the 19th century, the progressive elimination of the disease from Europe and North America in the middle years of the 20th century and final global eradication of smallpox in 1977. All this happened without the benefit of a controlled trial of the kind that would now be used for evaluating the efficacy of a newly developed vaccine.

Until the Smallpox Eradication unit carried out in 1967–1968 the work described earlier in this chapter, neither the potency of vaccines nor the methods of inoculation were standardized, so that the difficulty of evaluating vaccine efficacy and the duration of protection was often compounded by the use of vaccine of low potency or by unsatisfactory techniques. Even during the Intensified Smallpox Eradication Programme it was surprisingly difficult to obtain accurate and reliable data on the level of protection against variola major provided by vaccination. The reason for this is that allocation of an individual to the "vaccinated" category has always been made on the basis of the presence of a scar attributed to smallpox vaccination. Prior to the improvements in vaccine achieved after the Intensified Smallpox Eradication Programme was launched, such a scar was sometimes due to bacterial infection rather than the replication of vaccinia virus, especially in the Indian subcontinent, where the rotary lancet was widely used. In addition, studies in Pakistan by Heiner et al. (1971a) showed that many vaccinated persons living in endemic areas experienced subclinical attacks of smallpox, thus augmenting the protection conferred by vaccination.

The best available information, which almost certainly underestimated the protection afforded by vaccination, came from several sets of data on secondary attack rates among vaccinated and unvaccinated family contacts of smallpox cases in Bangladesh, India and Pakistan reviewed in Chapter 4 (see Table 4.12). Cases involving substantial numbers of contacts (100 persons) were selected and the rates of protection afforded by vaccination were calculated (Table 11.25); they varied between 90.7% and 97.1%. In these field studies neither the lapse of time since vaccination nor the potency of the vaccine as administered was known, so that it was impossible to determine the reasons for the occurrence of cases of smallpox among vaccinated contacts. The most likely reasons were the use of unsatisfactory vaccines many years earlier or a long period of time since primary vaccination in areas in which revaccination was uncommon.

When confronted with an outbreak of smallpox, it was usual for public health workers to vaccinate or revaccinate all close contacts of index cases (see Chapter 10). Some of these contacts would not then have been infected with variola virus, but others were probably incubating the disease. The studies just described provide some data on the protection provided by post-exposure vacci-

Table 11.25. Rate of protection afforded by vaccination

Location of outbreaks	Vaccination scar	Total number of contacts	Contacts developing smallpox		Rate of protection by vaccination[a] (%)	Reference
			Number	%		
Madras, India	–	103	38	36.9	96.7	Rao et al. (1968a)
	+	1 146	14	1.2		
Punjab Province, Pakistan	–	45	33	73.3	95.7	Heiner et al. (1971a)
	+	190	6	3.2		
Punjab Province, Pakistan	–	22	10	45.5	97.1	Heiner et al. (1971b)
	+	238	3	1.3		
Sheikhupura District, Pakistan	–	43	38	88.4	91.9	Mack et al. (1972a)
	+	180	13	7.2		
Calcutta, India	–	80	61	76.3	90.7	Mukherjee et al. (1974)
	+	661	47	7.1		

[a] Rate of protection by vaccination = $100\left(1 - \frac{\text{percentage of vaccinated contacts with smallpox}}{\text{percentage of unvaccinated contacts with smallpox}}\right)$.

Table 11.26. Effect of vaccination after exposure on occurrence of smallpox in family or household contacts

Vaccination status of contacts	Number of contacts	Cases of smallpox		Reference
		Number	%	
Primary vaccination after exposure	61	18	29.5	Rao et al. (1968a)
Never vaccinated	42	20	47.6	
Primary vaccination within 10 days of exposure	16	12	75.0	Mack et al. (1972a)
Never vaccinated	27	26	96.3	
Vaccinated or revaccinated within 7 days of exposure	52	1	1.9	Heiner et al. (1971b)
Never vaccinated	412	90	21.8	

nation (Table 11.26). Although the numbers are small and not statistically significant in some individual studies, all the analyses showed a lower rate of occurrence of smallpox in previously unvaccinated family contacts who were vaccinated after exposure. The level of protection was greater when previously vaccinated subjects were included (Heiner et al., 1971a). Even when post-exposure vaccination did not prevent the occurrence of smallpox, it often mitigated its severity. Rao (1972), for example, recorded that 8.8% of cases of smallpox occurring in subjects who underwent primary vaccination after exposure were of the modified type, compared with 1.1% among those never vaccinated and 24.7% among persons with scars of primary vaccination, but not vaccinated after exposure.

Mack et al. (1972) succinctly summarize their views on the determinants of infection with smallpox as follows:

"For contacts of any given vaccination status, the rates for protection did not vary with the age, sex or disease severity of the introducer, or with the age or sex of the contacts. Neither did they vary by season, by the closeness of the kinship between contact and introducer (i.e., siblings, cousins, uncle–nephew, etc.), by their housing relationship (i.e., same or different house within the compound), by caste, by occupation of the household head or by the house construction material."

Thus vaccination status was overwhelmingly the most important factor in determining the occurrence of infection.

Even though controlled trials were never carried out with smallpox vaccine, it is apparent that it was very effective in preventing smallpox. Clearly, a potent vaccine was required, so that protection was ensured, although such protection declined with the passage of time. Smallpox vaccination had the great advantage over most other types of immunization that it was very easy to deter-

mine when a successful take had been achieved, especially after primary vaccination, and the resulting scar provided permanent evidence of it. The general medical opinion, on which the International Health Regulations for smallpox vaccination were based, was that successful vaccination or revaccination within the previous 3 years provided virtually certain protection against smallpox.

CHAPTER 12

SOUTH AMERICA

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INTRODUCTION

When the Intensified Programme began, in 1967, South America presented the best prospects in the world for the eradication of smallpox. By that time, a single country, Brazil, was reporting almost all cases in the Americas (Table 12.1); and there was little reason to suppose that important areas of endemicity existed elsewhere, although the possibility that unreported foci of smallpox were present in other countries would have to be investigated. Brazil, although a very large and populous country, was small by comparison with the extensive endemic regions of Africa and Asia. Moreover, its relatively advanced health system and its wide-reaching transport and communications network offered promise that an effective programme could be conducted.

In the global strategy of eradication, it was logical to give priority to interrupting transmission in South America. Once that had been achieved, it should be easy to keep the continent free of smallpox because the risk of a case being imported from as far away as Africa or Asia was small. The resources initially available for the programmes in South America could then be released for use elsewhere.

A regional programme for the eradication of smallpox in the Americas had begun in 1950 pursuant to a resolution of the XIII Pan American Sanitary Conference (Pan American Health Organization, 1971a). This action was strongly supported by the Director of the Pan American Sanitary Bureau (see box), Dr Fred L. Soper, a vigorous proponent of the concept of eradication (Pan American Sanitary Organization, 1949). The decision was reached only 2 years after the commencement of the Bureau's programme to eradicate *Aedes aegypti*, the mosquito vector of yellow fever, from the Americas. Dr Soper considered the latter action to be a "landmark in international health...the first official recognition by an international health organization of regional responsibility for the solution of a

The Pan American Health Organization and the WHO Regional Office for the Americas

The origin of the Pan American Sanitary Organization (later known as the Pan American Health Organization—PAHO) dates from December 1902, when, at the First General International Sanitary Convention of the American Republics, a series of agreements pertaining to quarantine regulations for the Americas were adopted. To oversee their implementation, to receive reports from governments and to staff periodic meetings, a permanent executive body was created—the International Sanitary Bureau, subsequently renamed the Pan American Sanitary Bureau. Over the next 45 years, the Bureau's activities were largely concerned with this function. Its modest budget was covered by an annual subvention from each of its Member governments.

By virtue of a formal agreement with the World Health Organization, signed in 1949 and approved in the same year by the Second World Health Assembly, the Pan American Sanitary Bureau undertook to serve as the WHO Regional Office for the Americas, but, in deference not only to tradition but also to the continued existence of the Pan American Sanitary Organization, it would retain its own name and identity (Howard-Jones, 1980).

The regular budget of PAHO is financed from two sources: approximately one-third of the total is covered by an allotment from WHO deriving from the contributions of the Organization's Member States throughout the world; the remaining two-thirds are funded by the Member countries of PAHO.

health problem involving an entire continent" (Soper, 1951). The Pan American Health Organization (PAHO) assisted many countries in the development of laboratories to produce freeze-dried smallpox vaccine and many undertook mass vaccination campaigns, some with bilateral assistance.

By 1959, smallpox transmission had been interrupted in all but 5 countries of South America (Table 12.1), of which 3—Brazil, Colombia and Ecuador—were recording large numbers of cases every year. Between 1950 and 1959, the two latter countries had embarked on national programmes to attempt to eliminate the disease. In 1955 Colombia initiated a systematic mass vaccination campaign, which was completed in 1961. Ecuador began a similar campaign in 1958, which likewise ended in 1961. Bolivia, which recorded 7 cases in 1959, had just completed a 2-year mass vaccination campaign and appeared to be on the verge of interrupting transmission (Frederiksen et al., 1959). Argentina, with comparatively high levels of vaccinial immunity throughout the country as a result of intensive vaccination campaigns, reported only 36 cases in 1959, primarily in provinces adjacent to Brazil.

Between 1959 and 1966, Argentina, Bolivia, Colombia and Ecuador interrupted ende-

Table 12.1. Numbers of reported cases of smallpox in the Americas, 1959–1971[a]

Country	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971
Argentina	36	65	6	2	0	12	15	21	30[b]	0	0	24[b]	0
Bolivia	7	1	0	0	3[b]	5[b]	0	0	0	0	0	0	0
Brazil	4 840	6 561	8 526	9 763	6 467	3 168	3 417	3 623	4 514	4 372	7 407	1 771	19
Canada	0	0	0	1[b]	0	0	0	0	0	0	0	0	0
Chile	1[b]	0	0	0	3[b]	0	0	0	0	0	0	0	0
Colombia	950	209	16	41	4	21	149	0	0	0	0	0	0
Ecuador	1 140	2 185	496	204	45	0	0	0	0	0	0	0	0
French Guiana	0	0	0	0	0	0	0	0	0	1[b]	0	0	0
Paraguay	0	35	0	0	0	7[b]	32[b]	0	0	0	0	0	0
Peru	0	0	0	0	865	454	18	13	0	0	0	0	0
Uruguay	0	19[b]	1[b]	10[b]	1[b]	3[b]	1[b]	0	0	2[b]	3[b]	0	0
Venezuela	0	0	0	11[b]	0	0	0	0	0	0	0	0	0
Total	6 974	9 075	9 045	10 032	7 388	3 670	3 632	3 657	4 544	4 375	7 410	1 795	19

[a] Data from the WHO Smallpox Eradication unit based on special reports from governments and reviews of national data. The numbers differ slightly from some official reports published elsewhere (World Health Organization, 1980).

[b] Cases and outbreaks known or believed to have been imported.

Variola Major and Variola Minor

In most parts of the world in 1967, variola major was the variety of smallpox which was endemic. The much less severe variola minor was present in only 3 areas: South America, southern Africa and the Horn of Africa. Variola major had been endemic in most parts of South America since the 16th century, but in the early 1900s it had begun to be replaced by variola minor. The last known case of variola major occurred in Ecuador in 1962.

The differences in severity between the two forms of smallpox resulted in different responses by health authorities and patients when outbreaks occurred. Variola major was widely feared and its occurrence usually induced health authorities to respond vigorously with vaccination campaigns. In contrast, variola minor often tended to be regarded in the same light as measles or chickenpox. In fact, the disease was called alastrim in South America rather than smallpox. Patients with variola minor, instead of being confined to bed by the severity of the toxaemia, as with variola major, often remained mobile and thus were in contact with a greater number of susceptible persons. On the positive side, vaccination, even if performed long before, protected against variola minor more effectively than against variola major. The South American programme must be seen in this setting.

mic transmission. Few cases were detected in other countries, except Brazil and Peru, and most of those could be traced to importations from Brazil. In 1963, Peru, which had last recorded cases in 1954, experienced a serious setback when a major epidemic developed in Loreto Department in the Amazon basin adjacent to Brazil. Before detection, the outbreak had spread widely in the Amazon area and into the Andes and cases had occurred in Lima, the capital. A repeat vaccination campaign interrupted transmission in 1966.

By 1967, Brazil appeared to be the only endemic country in the Americas (Fig. 12.1). Uncertainty existed, however, because Brazil shares a border with all but two countries of South America and most border areas are in remote regions of the Amazon basin, in which there were few health centres to report cases if they did occur. The fact that all known cases were of the mild variola minor type made it less probable that outbreaks and cases, if present, would be detected and reported. However, in these sparsely populated areas, it seemed unlikely that the foci—if indeed they existed—would be extensive.

The eradication of smallpox in South America thus appeared to be a less formidable task than in other endemic regions of the world; primarily, it implied the interruption of transmission in Brazil. Indeed, of the continents in which smallpox had been en-

Fig. 12.1. South America: year of last endemic case of smallpox and number of reported cases occurring between 1967 and 1971 (figures in parentheses). The year shown for each country is that in which the continuing transmission of smallpox is believed to have ceased. Cases recorded in subsequent years are known or thought to have resulted from importations. Transmission in Peru ceased in 1954, but smallpox was reintroduced in 1963 and persisted through 1966.

Plate 12.1. Peruvian vaccinators pose under a banner at the conclusion of a training programme in 1968. Both smallpox and BCG (tuberculosis) vaccines were given; hence the banner reading "For a Peru Free of Tuberculosis and Smallpox".

demic in 1967, South America was the first to interrupt transmission. The last known case occurred in the city of Rio de Janiero on 19 April 1971.

REGIONAL STRATEGY AND ALLOCATION OF RESOURCES

From the point of view of cost-effectiveness and on epidemiological grounds the programme called for a concentration of available resources and support in Brazil, while providing to neighbouring countries such assistance as was required to develop surveillance and outbreak containment programmes in contiguous areas. If extensive endemic areas were found in neighbouring countries, additional resources could be provided. A more costly but arguably more reasonable approach would have added systematic vaccination campaigns in adjacent high-risk areas to create a partial barrier against the spread of smallpox. However, the strategy evolved along completely different lines.

Simultaneous mass vaccination campaigns throughout South America were proposed. The rationale is summarized in a report of the PAHO Secretariat to the XVII Pan American Sanitary Conference:

"...it is possible to eradicate smallpox in the Americas by immunizing the population at risk, within a relatively short time...although good coordination of all health services can be achieved for the smallpox eradication program or national smallpox vaccination programs, the same cannot be said of maintenance programs. This underlines the need to carry out smallpox vaccination programs simultaneously in as short a time as possible. If this is done and smallpox disappears, and good epidemiological surveillance services are established, then the intervals between revaccination may be gradually increased..." (Pan American Health Organization, 1967).

Conceptually, the strategy of mass vaccination did not differ from eradication programmes of previous decades. Epidemiological surveillance was considered to be important only after smallpox had disappeared. The traditional approach was deeply

Table 12.2. Latin America: WHO and PAHO expenditure for smallpox eradication, 1953–1971 (thousands of US$)[a]

Country	1953–1966	1967	1968	1969	1970	1971
Argentina	16	84	12	47	71	6
Bolivia	83	53	8	0	33	21
Brazil	198	328	481	382	244	176
Chile	0	75	21	0	0	10
Colombia	67	92	20	1	27	9
Cuba	0	4	0	15	36	1
Ecuador	183	0	44	8	20	14
Guatemala	0	0	0	0	18	8
Haiti	0	0	3	0	0	0
Honduras	38	10	0	0	0	0
Mexico	0	0	0	7	0	0
Paraguay	0	0	16	14	10	11
Peru	6	24	56	21	28	50
Uruguay	0	27	12	2	2	6
Venezuela	0	0	0	14	3	0
Others	51	0	0	0	0	0
Intercountry	338	90	168	182	126	220
Total	980	787	841	693	618	532
Percentage devoted to Brazil	20	42	57	55	40	33

[a] From WHO and PAHO financial records and vaccine distribution records.

ingrained and change was stubbornly resisted both by PAHO staff and by national programme directors. In Brazil, the detection of cases and the containment of outbreaks were introduced in some states only in 1969, and not until 1971 were these measures applied on a country-wide basis.

The provision in the plan to continue revaccination campaigns after the disappearance of smallpox may seem paradoxical, but it reflected the prevailing scepticism about the feasibility of eradication. Many health officials at that time believed that smallpox eradication could be achieved only if virtually all persons everywhere were vaccinated and periodically revaccinated. Experience with programmes for the eradication of malaria had shown that it was impossible to reach entire populations; for example, Indian tribes in the Amazon were rarely contacted by civil or health authorities. The concept that eradication could be achieved by stopping transmission of the virus without requiring everyone to be vaccinated was difficult to accept.

Because of the belief in the need for simultaneous mass vaccination throughout the continent, PAHO signed agreements with numerous countries—Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Paraguay, Peru, Uruguay and Venezuela—late in 1966 and early in 1967 which called for national vaccination campaigns. Some financial support was also provided by PAHO in certain years to Ecuador, Guatemala, Haiti, Honduras and Mexico. Special programmes were planned in all countries except Chile and Venezuela (in which maintenance vaccination was expected to be performed by the health services), the newly independent Guyana (formerly British Guiana), the French Overseas Department of French Guiana and the then Dutch colony of Suriname. For reasons which are not clear, Guyana was ignored and no special contact was made with either the French or the Dutch government until the end of the programme, when the authorities concerned were requested to cooperate in certifying the absence of smallpox.

WHO and PAHO expenditures (including the value of vaccine distributed) in support of national programmes reflected the strategy (Table 12.2). In 1967, 9 countries received financial support through PAHO; of the total expenditure, only 42% were earmarked for the programme in Brazil.

Mass vaccination campaigns of some form were eventually conducted in 8 countries (see box). The data available for these campaigns are incomplete, consisting primarily of numbers of vaccinations reported to have been performed in different areas. Few campaigns undertook more than perfunctory field assessments to determine the proportion of persons actually vaccinated and the proportion of vaccinations which were successful. Areas in which reasonably extensive mass campaigns were conducted are shown in Fig. 12.2.

A. URIBE

Plate 12.2. Peru conducted an extensive vaccination campaign throughout the departments of the Amazon basin where the risk of importations of smallpox from Brazil was greatest. In these areas, the teams relied heavily on boats for transport, like the specially assigned launch shown here.

Fig. 12.2. South America: areas in which systematic mass vaccination programmes were completed, 1967 – 1972.

The total number of vaccinations reported to have been performed in each of the countries, both in mass campaigns and by the established health services, is shown in Table 12.3.

Only Chile, French Guiana, Paraguay and Suriname did not conduct some type of special vaccination campaign, and, with the exception of Paraguay, there was little motivation or need for them to do so. Chile had no border with Brazil and was thus at minimal risk of imported smallpox, while French Guiana and Suriname, with small populations mainly settled along the coast, had scarcely any communication with Brazil.

Paraguay, on the other hand, sharing a border with Brazil and receiving many travellers from that country, was at unusually high risk. Because of fiscal constraints, however, it was unable to carry out a special programme. A mass vaccination campaign had been conducted between 1958 and 1960, during which 86% of the population was said to have been vaccinated. After that time, routine vaccination was offered in health centres. During May and June 1971, a WHO–Paraguay team conducted a search for cases and also performed scar surveys in several

Table 12.3. South America: population and number of reported smallpox vaccinations, 1967–1972 (thousands)[a]

Country	Population (1970)	Number of vaccinations[b]					
		1967	1968	1969	1970	1971	1972
Argentina	23 962	1 808	324	2 141	11 009	1 545	844
Bolivia	4 325	1 142	320	442	490	412	211
Brazil	95 847	17 984	21 406	25 851	37 325	18 010	13 883
Chile	9 368	1 557	1 520	1 304	1 150	942	747
Colombia	20 803	2 307	5 236	4 521	3 582	1 243	1 825
Ecuador	5 958	508	1 114	931	946	756	277
French Guiana	48	..	..	..	5	5	..
Guyana	709	5	12	17	536	12	6
Paraguay	2 290	167	183	214	338	329	357
Peru	13 193	2 222	1 677	2 195	2 631	2 118	2 419
Suriname	372	..	..	..	21	13	25
Uruguay	2 808	299	503	443	546	361	174
Venezuela	10 962	1 502	1 593	1 379	1 119	869	786

[a] From Rodrigues (1975); population figures from United Nations (1985). The number of vaccinations reported annually by each country includes both those performed during special mass vaccination campaigns and routine vaccinations given in hospitals, clinics and other health units.

[b] .. = Data not recorded.

Table 12.4. Paraguay: proportion of persons, by age group (years), with vaccination scars in 4 districts, 1971[a]

District	Number surveyed	% with vaccination scars		
		⩽4	5–14	⩾15
Asunción	15 033	47	88	88.5
Paraguarí	744	69	88	84
San Lorenzo	2 480	34.5	72.5	68.5
Villa Hayes	1 183	18	72	79

[a] From WHO/SE/72.38.

areas to assess the level of immunity (*Wkly epidem. rec.*, 1971a; Table 12.4). No cases of smallpox were found, and 78.5% of those surveyed bore vaccination scars. It was apparent that the existing health services had done reasonably well in sustaining immunity. A costly special campaign might have improved the levels of immunity, at least among young children, but, as was apparent in retrospect, it was not needed.

Information about smallpox in South America from 1967 to 1971, other than in Brazil, is fragmentary. Little was done until 1971 to improve reporting systems, and the investigation of cases was often perfunctory. Uruguay promptly detected and documented 4 importations in 1968 and 1969, and French Guiana similarly dealt with 1 importation in 1968, but these were the exceptions. In Argentina, nothing is known of the 30 reported cases in 1967, which may have been importations, mistaken diagnoses or a combination of both. Argentina's outbreak of 24 cases in 1970 was actually discovered and investigated by Brazilian teams, who subsequently informed the Argentine health authorities of the occurrence. An episode in Colombia illustrates that even cases diagnosed as smallpox by health staff were sometimes not reported to the national authorities. In 1971, during a special search for possible undetected cases in the Amazon basin, a WHO–Colombia team was informed by a hospital director of 4 cases of smallpox which had been diagnosed in November 1970 in a border town. No report of these cases had been forwarded. The team discovered that the cases concerned were actually misdiagnosed cases of chickenpox, but no one knows how many other outbreaks may have been detected and not reported during earlier years in this and other parts of the Amazon basin. That these isolated regions contained many susceptible individuals was documented by the WHO–Colombia team, which conducted a scar survey in a suspect area. Less than 20% of the children under 5 years of age had ever been vaccinated; among those aged 5–14

Special Vaccination Campaigns Between 1967 and 1972 in South America, excluding Brazil

Argentina (1970 population, 23 962 000): Campaigns were conducted on a province-by-province basis with high levels of vaccination coverage in some provinces and less than 50% in others. The first to be vaccinated were the inhabitants of some provinces in the north, bordering on Brazil, and of provinces in the far south of the country. Subsequent provincial campaigns followed in no logical sequence; no campaign was conducted in the capital or the vast area constituting Buenos Aires Province. In all, some 7.8 million vaccinations were reported to have been performed during the campaign.

Bolivia (1970 population, 4 325 000): Bolivia had conducted a mass campaign in 1957–1958 during which 2.4 million persons had been vaccinated, a figure equivalent to about 75% of its population at that time. During a repeat campaign, begun in 1963 and concluded at the end of 1968, 3.7 million people were vaccinated, a figure equivalent to 81% of the population. A third campaign was initiated in 1969, with most of the resources concentrated in 6 of the country's 8 departments (those adjacent to Brazil). The number of people reported to have been vaccinated was equivalent to 82% of the population of the 6 departments concerned.

Colombia (1970 population, 20 803 000): Between August 1967 and the end of 1972, campaign staff performed 13.2 million vaccinations in the highland areas. No campaigns were conducted in the Amazon basin adjacent to Brazil, the area at greatest risk.

Ecuador (1970 population, 5 958 000): During vaccination campaigns conducted throughout the country, 5 million vaccinations were recorded between 1967 and 1972. A survey conducted in 45 localities in 1972 revealed the presence of vaccination scars in 41% of individuals under 5 years of age, in 85% of those aged 5–14 years, and in 88% of those aged 15–19 years.

Guyana (1970 population, 709 000): A mass campaign was conducted in 1970 during which 536 000 persons were reported to have been vaccinated.

Peru (1970 population, 13 193 000): A special campaign in Peru was conducted in 1967–1972, primarily in the eastern departments of the country bordering on Brazil and in other departments considered to have the least adequate health services. During the campaign, 5.6 million vaccinations were reported to have been performed.

Uruguay (1970 population, 2 808 000): Personnel of the existing health facilities performed most of the vaccinations, recording 1.3 million in all, during the period 1967–1971. An additional 650 000 vaccinations were given in the course of special campaigns. Until 1971 the thermolabile liquid vaccine rather than the freeze-dried product was used and many of the vaccinations were thought to have been unsuccessful.

Venezuela (1970 population, 10 962 000): A well-organized and well-evaluated vaccination campaign was conducted throughout most of Bolívar State from August to November 1970 and from April to June 1971. This was a high-risk area bordering on Brazil in which the population was scattered and access to health facilities was limited. Among the 289 000 residents, a vaccination coverage of 91.6% was achieved.

years living in rural areas, only half had previously been vaccinated. From these and other data collected during the period 1971–1973, it was concluded that smallpox had not been sustained in the sparsely populated Amazon border areas. However, neither surveillance nor high levels of vaccinial immunity played a significant role in the attainment of this smallpox-free status.

THE PROGRAMME IN BRAZIL

During the 1950s Brazil, unlike other countries in the Americas, conducted no nation-wide vaccination campaigns. Local authorities, according to their interest and motivation, vaccinated people in cities and towns when there were outbreaks, but no

Plate 12.3. Posters were produced in many countries. This one in Colombia says, "Smallpox vaccine protects the whole family".

programme was carried out in the country as a whole. Between 1950 and 1960, comparatively few cases of smallpox were recorded for a country so populous, the number ranging from a low of 749 in 1950 to a high of 6561 in 1960. However, reports of cases at that time were received from only a few rural health units operated by a special government service and from some hospitals in state and territorial capitals. In fact, only a single city, São Paulo, had a reasonably comprehensive reporting system (Morris et al., 1971). Thus, the actual number of cases was almost certainly many times greater than that recorded.

In 1958, Brazil had joined other PAHO Member States in adopting a resolution of the XV Pan American Health Conference to eliminate smallpox from the Americas. This action was reaffirmed in 1961 by the Charter of Punta del Este, which called on all governments in the Americas to take immediate action "to eradicate malaria and smallpox from the Hemisphere" (Pan American Health Organization, 1973). Shortly afterwards the Oswaldo Cruz Institute in Rio de Janeiro began the manufacture of freeze-dried vaccine.

In 1962, Brazil launched a national campaign against smallpox (Rodrigues, 1975). By the end of 1965, 24 million vaccinations had been performed in a population of 84 million. The initiative for the campaign rested with the authorities of the separate states and territories, few of which were strongly motivated. Not many of the staff were employed at the federal level and only one of them travelled to the field to assist states in developing and monitoring programmes. The campaign was considered to have been satisfactorily executed in no more than 4 of the 27 states and territories. The number of reported smallpox cases throughout the country decreased from 9763 in 1962 to 3623 in 1966. However, because the reporting system had shown little improvement over this period, the decreasing incidence figures meant little.

Interest in the programme heightened in 1965 with the introduction of a new vaccination technique—the jet injector gun. With assistance from PAHO, a special pilot programme was undertaken in the northern Amazonian territory of Amapá by a combined Brazilian–United States Communicable Disease Center team. The team members evalu-

Smallpox Cases in the Americas, Excluding Brazil, after 1966

Outside Brazil, only 60 cases of smallpox were reported in the Americas after 1966. All were in areas adjacent to Brazil. Except for 30 cases in northern Argentina in 1967, when sources of infection were not identified, all could be traced to importations. Because surveillance was poor throughout the areas neighbouring Brazil, other importations probably occurred but did not result in sustained transmission.

- *Argentina* (1967): Thirty reported cases of which 27 were in Misiones Province, which borders on Brazil, 2 in Formosa Province and 1 in Santa Fé Province, both of which provinces are in the north of Argentina although some 400 kilometres from the nearest endemic Brazilian areas. None of the cases was investigated nor were efforts made to trace the source.
- *French Guiana* (1968): One case, in a Brazilian traveller, in the Amazonian area of the country (*Wkly epidem. rec.*, 1968a).
- *Uruguay* (1968, 1969): Two cases in 1968 and 3 in 1969 resulting from 4 importations from the adjacent, heavily endemic state of Rio Grande do Sul, Brazil. Only 1 secondary case occurred.
- *Argentina* (1970): Twenty-four reported cases between April and June in the border town of Colonia Alicia, Misiones Province. The outbreak was detected by epidemiologists from Rio Grande do Sul State, Brazil. The first case, in a 19-year-old man, was diagnosed in a Brazilian hospital situated 100 kilometres from Colonia Alicia. The patient reported having been exposed to cases in Argentina. Investigations, carried out first by a Brazilian team and subsequently by Argentine authorities, revealed an outbreak of 24 cases which had occurred after importation from a nearby Brazilian border town (*Wkly epidem. rec.*, 1970c). Following containment of the outbreak, Argentina undertook a mass vaccination campaign in Misiones and the neighbouring provinces, during which 443 000 people (84% of the population) were vaccinated (Rodrigues, 1975).

Table 12.5. Brazil: comparison of vaccination campaigns using the multiple pressure technique (Belém) and the jet injector (Macapá)

	Belém[a]	Macapá[b]
Estimated population	450 000	35 700
Number of persons vaccinated	411 000	32 700
Coverage (%)	91.3	91.6
Number of workers	1 200	50
Number of person-days	6 010	126
Number of vaccinations per person-day	68.4	259.5
Percentage of successful vaccinations	80.0	90.0
Number of vehicles used	50	2
Total cost of campaign	US$27 520	US$708
Average cost per dose	US$0.067	US$0.022

[a] Door-to-door vaccination.
[b] Vaccination at established sites and by mobile units, as well as door-to-door.

ated the cost and efficacy of vaccination with jet injectors in relation to vaccination utilizing the conventional multiple pressure technique (Millar et al., 1971) (Table 12.5). With the use of the jet injector an average of 259.5 persons were vaccinated per worker-day, compared with a corresponding figure of 68.4 when the multiple pressure technique was employed. The cost per vaccination was US$0.022 with the jet injectors and US$0.067 using multiple pressure vaccination. Moreover, the jet injectors produced a higher proportion of successful vaccinations. The members of the group responsible for the trial were enthusiastic and recommended a renewed effort to eradicate smallpox. They proposed that a federal director and staff should be appointed to help to organize and

BY COURTESY OF D A HENDERSON

Plate 12.4. The demonstration in 1965 of the efficacy of the jet injectors provided an important stimulus to Brazil to undertake an effective national smallpox programme. This device could vaccinate as many as 1000 persons each hour.

execute state vaccination campaigns throughout Brazil, and that jet injectors should be provided in order to complete the campaigns, as they stated, "in months instead of years". It was also recommended that state personnel should immediately be selected and trained in the organization of surveillance programmes, a recommendation that was sound in principle but destined to be ignored.

DEVELOPMENT OF THE BRAZILIAN NATIONAL PROGRAMME, 1966

The demonstration by the Amapá team of the efficacy of the jet injector and the decision in May 1966 by the Nineteenth World Health Assembly to undertake an intensified global eradication programme persuaded the Brazilian authorities to begin a new national programme.

On 31 August 1966, a federal decree was promulgated which required an intensification and coordination of public and private activities throughout the country to combat smallpox in all its clinical forms with a view to achieving the eventual eradication of the disease. The aim was to conduct a mass vaccination campaign among the population at large, state by state. It was expected that a surveillance system would be developed to detect and contain outbreaks but surveillance was not intended to begin until each state had completed its vaccination campaign.

Federal financial assistance was given to augment vaccine production at the Oswaldo Cruz Institute (Rio de Janeiro) and plans were formulated for the development of freeze-dried vaccine production at the Institute for Biological Research (Pôrto Alegre) and the Butantan Institute (São Paulo). To aid these laboratories, as well as others in the Americas, PAHO arranged for the Connaught Laboratories of Toronto, Canada, to serve as a reference laboratory to certify vaccine potency and purity and to provide the staff of the assisted laboratories with technical support and training (see Chapter 11).

Provision was made for additional staff for the Brazilian programme. Twelve full-time professional workers—8 medical officers and 4 administrative staff were assigned to the national eradication programme by the federal Foundation of Special Public Health Services. Foundation personnel, in contrast to most employees of the national health ser-

vice, were paid sufficiently large salaries to permit them to work full time in the campaign. PAHO was asked to recruit 3 medical epidemiologists and a statistician, and to provide 26 vehicles and 72 jet injectors, as well as equipment for the vaccine production centres. Vaccination was to be undertaken state by state, with the great majority of field workers to be locally recruited and trained, and discharged when the programme was completed. Workers were expected to have had 6 years of education and supervisors 12 years. Those performing especially well as supervisors and on the assessment teams were to be retained for service in other states.

The programme was launched in November 1966, and by the end of the year 452 000 persons had been vaccinated. Although it was a hopeful beginning, the subsequent development of the programme was hampered by erratic federal commitment, frequent changes in leadership and serious problems with the quantity and the quality of vaccine produced. The outcome, only a few months before the last case occurred, was anything but certain.

THE BEGINNING OF THE VACCINATION CAMPAIGN, 1966–1967

The initial plan called for a campaign (Table 12.6) which in 3 years would reach more than 90% of Brazil's population (95.8 million in 1970). The projected targets were highly ambitious and not until the last quarter of 1969—fully 3 years after its commencement—did the programme achieve the expected momentum (Fig. 12.3). In an endeavour to meet these desired targets, virtually all the time and energy of the staff were directed to the vaccination campaign.

The initial smallpox campaigns were conducted in the north-eastern states, in which socio-economic conditions were the least favourable, operational problems were the most difficult and smallpox incidence was deemed to be the highest (Fig. 12.4). Three states (Sergipe, Rio Grande do Norte and Pernambuco), with a total population of more than 7 million, were thought to have been sufficiently well vaccinated (80% reported coverage) during the 1962–1966 campaign not to need a repeat programme. Only a portion of Piaui State was considered to require vaccination. Alagoas (population 1.6 million), crucially situated between Pernambuco and Sergipe, was selected as the state in which to initiate

Table 12.6. Brazil: numbers of vaccinations planned and performed in the mass campaign, 1966–1971 (millions)[a]

Period	Vaccinations planned	Vaccinations performed
1966–1968	34.5	19.2
1969	39.1	20.9
1970	18.0	31.6
1971	0	12.1
Total	91.6	83.7

[a] Does not include routine vaccinations reported by health units.

operations. An experienced staff, consisting of 60 vaccinators, 16 drivers, 12 team leaders, 1 jet injector technician, and 3 supervisors, launched the campaign at the beginning of the rainy season, in November 1966, and concluded it 5 months later. Meanwhile, campaigns had begun in the rest of Piaui (January), Paraíba (February), Ceará (May) and, at the end of the year, in Rio de Janeiro State. In June, smallpox cases were hospitalized in the federal capital, Brasília, and 34 cases occurred in outbreaks in neighbouring areas. Because of this, a campaign was initiated in Brasília (June) and in the neighbouring state of Goiás (September). Although the outbreak was small and the attention it received was perhaps not warranted, the

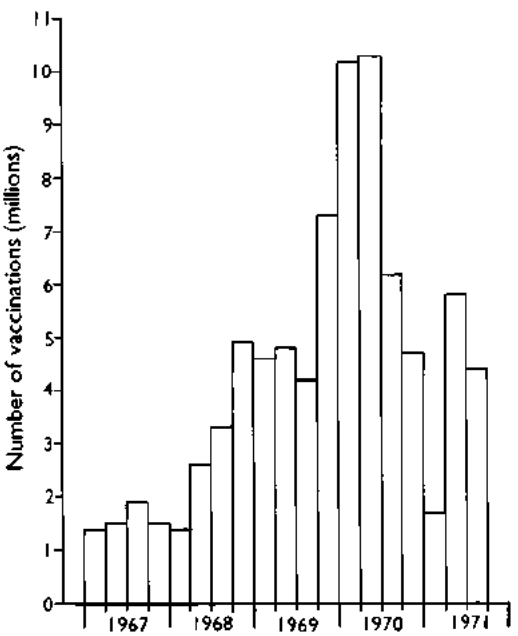

Fig. 12.3. Brazil: number of vaccinations performed by trimester, 1967–1971.

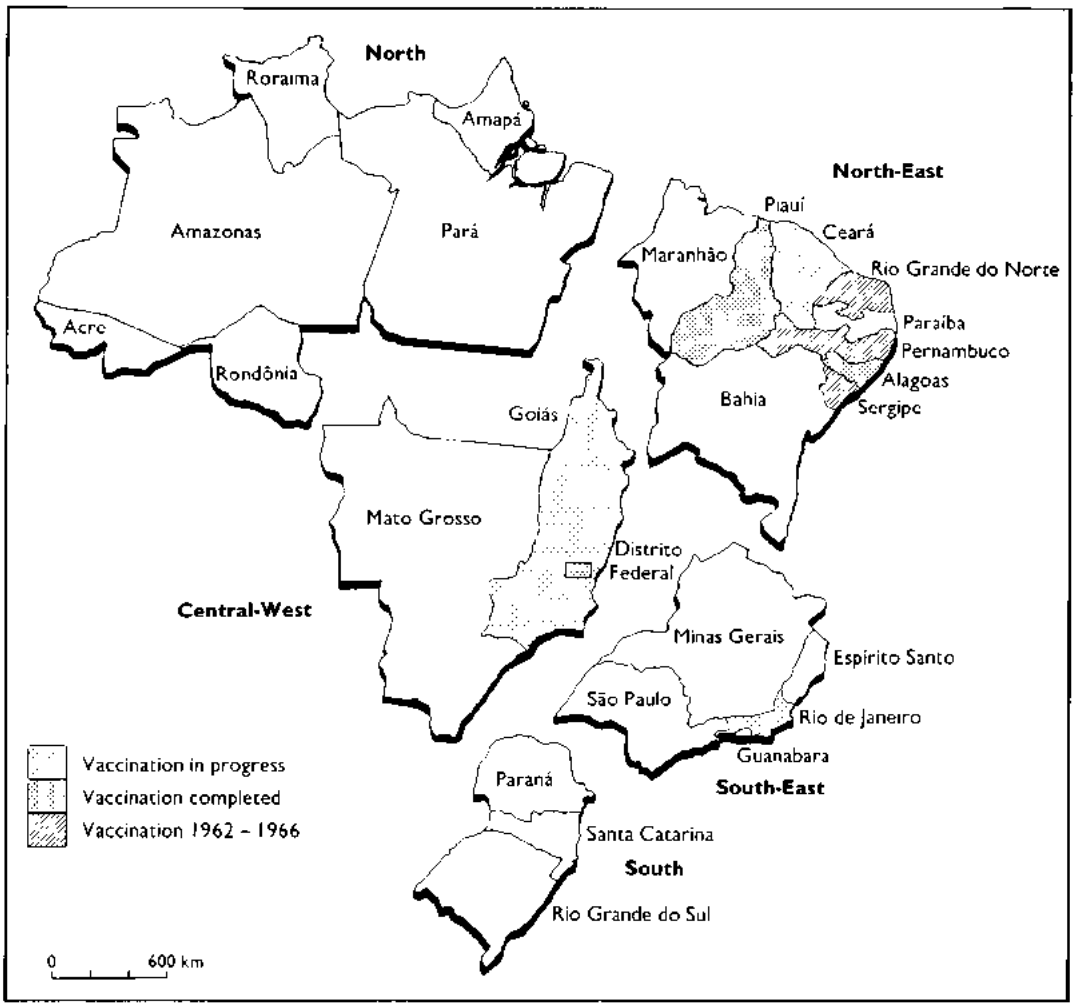

Fig. 12.4. Brazil: status of the smallpox vaccination programme, by region, December 1967.

publicity associated with a campaign in the federal capital was helpful in promoting the programme nationally.

The vaccination campaign within states was undertaken on a *município*-by-*município* basis (as an administrative unit a *município* corresponds roughly to a county in the USA). There were then some 4000 *municípios* in Brazil. An intensive vaccination campaign of several days' duration was conducted in each *município* before the team or teams moved to the next. The inhabitants of the state capitals were usually the first to be vaccinated, after which the teams moved to more sparsely populated areas. Each team consisted of 4 or 5 vaccinators, a leader and a driver. Groups of 4 teams were directed by an area supervisor. Jet injectors were used for vaccination at collecting points in both urban and rural areas. When bifurcated needles became available in 1968, they were used primarily in rural areas. All individuals aged 3 months and over were vaccinated.

The Outbreak in Branquinhas

Although progress in terms of numbers vaccinated was far less in 1967 than had been expected, a more serious problem came to light in July of that year. Twenty-one cases of smallpox were reported from the town of Branquinhas, Alagoas State, which had completed its systematic vaccination campaign only 3 months before. The *município* of Branquinhas had a population of 6317, of whom 1435 lived in the town. A vaccination team had spent 6 days in the *município* and reported that it had performed 6558 vaccinations, a

CENTERS FOR DISEASE CONTROL, 1965

Plate 12.5. Leo Morris (b. 1935), a statistician, worked with Henderson at the Communicable Disease Center during 1966 for the programme in western and central Africa. He joined the programme in Brazil in 1967 as a WHO staff member and was instrumental in developing the national weekly surveillance report and in promoting the investigation of outbreaks, including the one at Branquinhas, which demonstrated the need for continuing assessment of the vaccination campaign.

number larger than the estimated population. There seemed to be only two likely explanations: either many vaccinations had been unsuccessful because of substandard vaccine or poor technique, or the number of reported vaccinations was exaggerated.

Staff attached to the national campaign investigated immediately and found not 21 but 51 cases of smallpox. Only 2 cases had previously been vaccinated (Morris et al., 1970b). A survey of randomly selected households in the city revealed that vaccination take rates were satisfactory but that only 49% of the inhabitants had actually been vaccinated by the teams. Surveys in two rural areas showed that 75% of the residents had been vaccinated in one of them and nobody in the other. It was apparent that records had been falsified and that supervision and planning were poor.

The Repercussions of the Branquinhas Outbreak

Until the Branquinhas outbreak, the national programme director had refused to assign even a few personnel and vehicles to "do nothing but evaluate", as he expressed it. As in many other programmes, it was believed that all possible resources should be deployed in administering vaccine. Branquinhas was a turning-point. It was agreed that assessment teams must be created, and these began work early in 1968 (*Wkly epidem. rec.*, 1968c). Each comprised 4 persons, who visited vaccinated areas about 7–9 days after the completion of a programme. A household probability survey was conducted, in which, in a sample of households, the vaccination coverage of all household members was determined, as were the take rates for primary vaccination among children between 3 months and 5 years of age (Lavigne de Lemos & Morris, 1969). With improved supervision and a knowledge that their work was being continually assessed, the teams consistently achieved much better vaccination coverage. The data from 26 *municipios* in 2 states—Minas Gerais and São Paulo—compiled in 1969 illustrate this (Table 12.7).

In most *municipios*, independent assessment showed that more than 90% of individuals aged between 3 months and 14 years—the age group in which three-quarters of all cases occurred— had been vaccinated. The proportion of older persons vaccinated during the campaign tended to be lower, but a great many of them had already had smallpox or had been vaccinated at some time in their lives. In areas in which less than 80% of those under 5 years of age were found to have been vaccinated, a repeat vaccination campaign was

Table 12.7. Brazil: results of vaccination assessment in 26 *municipios* in 2 states[a]

Population age group	Number of *municipios*			
	With over 90% of population vaccinated	With 80–90% of population vaccinated	With 70–80% of population vaccinated	With under 70% of population vaccinated
3 months–4 years	21	3	2	0
5–14 years	23	0	2	1
15–44 years	18	5	1	2
⩾45 years	11	11	2	2

[a] From *Wkly epidem. rec.* (1969d).

BY COURTESY OF D.A. HENDERSON, 1966

Plate 12.6. Oswaldo José da Silva (b. 1907), in the centre, was director of the national programme in Brazil, 1967–1968. A former malariologist and PAHO staff member, he was a skilful administrator and was responsible for the establishment of Brazil's national vaccination campaign structure. With him are K.S. Ramakrishnan from the WHO Regional Office in New Delhi and John Copland, administrative officer of the Smallpox Eradication unit in Geneva from 1967 to 1977.

conducted. Primary take rates were usually above 90%, although when revaccination responses were checked, the take rates were usually only 50–60%. Considering the low potency and lack of stability of the vaccine used (see below), the results were surprisingly good.

Because the programme was making less progress than had been planned, and because of the Branquinhas incident, a new director, Dr Oswaldo da Silva, was appointed in September 1967. Dr da Silva had worked in both Brazil and PAHO in the malaria eradication programme and was widely respected for his skills in management and his grasp of logistics. Following his appointment, a more effective organizational structure began to take shape.

Critical to the ultimate success of the programme was the establishment in May 1967 of a national smallpox reporting system and the publication each week of a surveillance report (*Boletim semanal da Campanha de Erradicação da Variola*), which documented the numbers of cases reported each week, described developments in the programme and recorded the results of investigations by field staff (WHO/SE/73.52, Lavigne de Lemos & Souza). Fostered by an imaginative young WHO epidemiologist-statistician, Mr Leo Morris, it was modelled on reports of surveillance programmes at the United States Communicable Disease Center, in which he had previously worked. This simple mimeographed report was sent to more than 2000 senior health and programme staff. It served to instruct, to motivate and to give the widely scattered staff a sense of common purpose.

With repeated reminders to states to report cases each week on standardized reporting forms, the notification system gradually improved, but it was apparent from the several field investigations conducted that few of the many cases were being detected. Some of these investigations revealed significant problems. One was an outbreak in a 250-bed children's hospital in Vitória, Espírito Santo State, which was reported in October 1967. Investigation revealed that 51 cases had occurred over a 10-month period. During this time, there had been at least 11 and perhaps 14 separate introductions of smallpox into the hospital; between 36 and 40 children were infected there subsequent to admission for other causes. None of the children had ever been vaccinated; 5 died (Morris et al., 1970a). That hospitals served as important foci for disease transmission was subsequently to be documented repeatedly in Brazil and elsewhere. The proper isolation of patients and the vaccination of staff and of patients on admission to hospital were seldom effectively practised.

By the end of 1967, work had been completed in the Federal District, Piauí and Alagoas. More support was obviously required, and the Ministry of Health requested WHO to provide 178 vehicles (in addition to the 26 which had been supplied in 1965) and 97 jet injectors (in addition to the 122 then in use). Of great help in Brazil was the minimum time-lag between the decision to provide vehicles and their availability. Locally manufactured vehicles could be delivered within weeks of placing an order, whereas in other parts of the world 12–24 months might elapse between order and delivery. The requested supplies arrived early in 1968.

THE VACCINATION CAMPAIGN GAINS MOMENTUM, 1968

Under Dr da Silva's leadership, the monthly numbers of vaccinations steadily increased

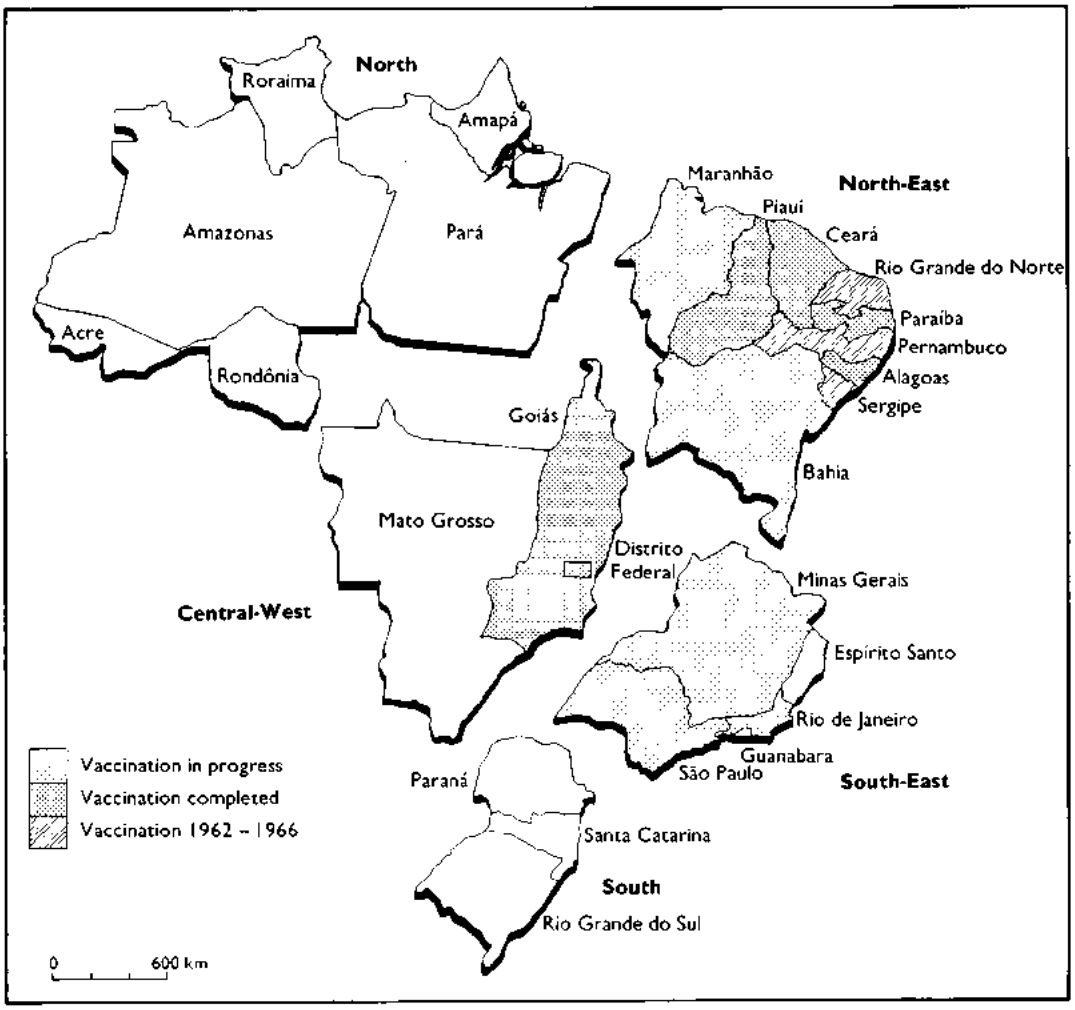

Fig. 12.5. Brazil: status of the smallpox vaccination programme, by region, December 1968.

during 1968; and with a programme of assessment in operation, there was a greater degree of confidence that the numbers reported were accurate. In addition, in states in which the systematic vaccination campaign had been completed, the staff began to investigate some of the cases reported. Virtually nothing was done, however, to strengthen surveillance in the states in which vaccination campaigns had not been conducted.

More than 12 million vaccinations were given in 1968—almost twice as many as in 1967 (Table 12.8). Fully 1000 staff were active in the field. Work was completed in 3 of the 4 states in which vaccination campaigns had been initiated in 1967, and programmes were begun in 3 additional states (Fig. 12.5) (*Wkly epidem. rec.*, 1968b).

The number of reported cases of smallpox showed little change (4372 in 1968 compared with 4514 in 1967), but because reporting was thought to be more complete the staff were encouraged (Table 12.9).

However, at the end of 1968, the government, as a general economy measure, made substantial cuts in the budget for the programme: per diem payments for Brazilian national staff were eliminated, thus curtailing travel; supplementary payments which had permitted senior staff to work full time in the programme were stopped; and the complement of programme staff was reduced to 759. Nearly 9 months elapsed before full support for the programme was resumed. Dr da Silva's target of 5 million vaccinations per quarter or 500 000 vaccinations per week was not to be achieved for another year.

Table 12.8. Brazil: number of vaccinations performed during the smallpox eradication programme, 1967–1971

States and territories	Population[a]	Number of vaccinations					Total 1967–1971
		1967	1968	1969	1970	1971	
North							
Rondônia	116 620	0	0	0	86 183	2 464	88 647
Acre	218 006	0	0	0	139 718	14 745	154 463
Amazonas	960 934	0	0	0	742 526	26 631	769 157
Roraima	41 638	0	0	0	16 684	14 992	31 676
Pará	2 197 072	0	0	0	1 602 725	158 139	1 760 864
Amapá	116 480	0	0	0	92 811	7 505	100 316
North-east							
Maranhão	3 037 135	0	1 106 633	1 186 059	0	0	2 292 692
Piauí	1 734 865	326 170	0	0	0	1 497 319	1 823 489
Ceará	4 491 590	2 528 610	1 180 433	0	0	0	3 709 043
Rio Grande do Norte	1 611 606	0	0	0	0	1 495 980	1 495 980
Paraíba	2 445 419	1 525 083	794 501	0	0	0	2 319 584
Pernambuco	5 252 590	0	0	0	0	5 025 094	5 025 094
Alagoas	1 606 174	1 263 293	0	0	0	1 517 295	2 780 588
Fernando de Noronha	1 311	0	1 240	0	0	0	1 240
Sergipe	911 251	0	0	0	844 664	0	844 664
Bahia	7 583 140	0	1 355 157	2 193 609	2 809 133	0	6 357 899
South-east							
Minas Gerais	11 645 095	0	995 926	5 241 195	4 150 537	0	10 387 658
Espírito Santo	1 617 857	0	0	1 455 393	0	0	1 455 393
Rio de Janeiro	4 794 578	69 698	3 483 458	396 595	0	0	3 949 751
Guanabara	4 315 746	0	0	0	356 656	1 310 891	1 667 547
São Paulo	17 958 693	0	1 693 341	5 943 675	8 046 401	0	15 683 417
South							
Paraná	6 997 682	0	0	3 320 015	4 065 097	0	7 385 112
Santa Catarina	2 930 411	0	0	0	2 855 306	0	2 855 306
Rio Grande do Sul	6 755 458	0	0	1 132 218	5 395 154	0	6 527 372
Central-west							
Mato Grosso	1 623 618	0	0	0	433 603	1 008 169	1 441 772
Goiás	2 997 570	507 878	1 613 237	0	0	0	2 121 115
Distrito Federal	546 015	374 914	0	0	0	0	374 914
Brazil							
Total population	94 508 554						
Total vaccinations—mass campaign		6 595 646	12 223 926	20 868 759	31 637 198	12 079 224	83 404 753

[a] As at census taken on 1 November 1970. United Nations (1985) data show a total population of 95 847 000 for Brazil in 1970 (see Table 12.3).

Table 12.9. Brazil: number of reported cases of smallpox, by states and territories, 1967–1972

States and territories	1967	1968	1969	1970	1971	1972
North						
Rondônia	0	0	0	0	0	0
Acre	0	0	0	0	0	0
Amazonas	13	5	4	0	0	0
Roraima	0	7	1	0	0	0
Pará	9	4	2	0	0	0
Amapá	0	24	2	0	0	0
North-east						
Maranhão	62	51	4	0	0	0
Piauí	9	9	0	0	0	0
Ceará	178	120	2	0	0	0
Rio Grande do Norte	0	4	0	0	0	0
Paraíba	139	112	0	0	0	0
Pernambuco	1	0	0	0	0	0
Alagoas	98	3	0	0	0	0
Fernando de Noronha	0	0	0	0	0	0
Sergipe	0	0	97	109	0	0
Bahia	214	612	2 140	389	0	0
South-east						
Minas Gerais	95	392	1 402	114	0	0
Espírito Santo	228	157	384	0	0	0
Rio de Janeiro	81	74	19	7	0	0
Guanabara	36	69	34	18	19[a]	0
São Paulo	2 261	1 598	1 432	114	0	0
South						
Paraná	137	218	992	56	0	0
Santa Catarina	158	93	11	28	0	0
Rio Grande do Sul	384	459	836	932	0	0
Central-west						
Mato Grosso	37	19	21	1	0	0
Goiás	342	321	14	0	0	0
Distrito Federal	32	21	10	3	0	0
North	22	40	9	0	0	0
North-east	701	911	2 243	498	0	0
South-east	2 701	2 290	3 271	253	19	0
South	679	770	1 839	1 016	0	0
Central-west	411	361	45	4	0	0
Brazil, total	4 514	4 372	7 407	1 771	19	0

[a] The last case occurred in April.

THE BEGINNING OF AN EFFECTIVE SURVEILLANCE PROGRAMME, 1969

The concept of assigning at least one epidemiologist to every state, to be responsible for the development of a system which would ensure the prompt transmission of weekly reports of cases from reporting centres and to investigate and contain outbreaks, had been increasingly stressed by the WHO Smallpox Eradication unit. However, neither the Brazilian nor the PAHO staff showed interest. Meanwhile, the efficacy of surveillance-containment activities had become increasingly apparent in eradication programmes, particularly in western Africa. With the aim of stimulating interest in the development of a surveillance programme, a special meeting of all of WHO's smallpox advisers in the Region had been convened in Rio de Janeiro in April 1968, in which Brazilian national staff also participated. It proved to have little impact.

Finally, in October 1968, Dr Nelson Morais, newly appointed as General Secretary of the Ministry of Health and himself an epidemiologist, was contacted by WHO and persuaded that a special effort should be made to develop a surveillance programme for smallpox which might eventually extend to other infectious diseases. At his urging, a special training programme in the surveillance and epidemiology of smallpox was conducted in São Paulo during January 1969 (*Wkly epidem. rec.*, 1969d). Instruction was provided by staff from the smallpox eradication programme, the Adolfo Lutz Institute and Mr Morris. Those who attended included 15 of the medical officers attached to the smallpox eradication programme who had

I. VEHNES, 1970

Plate 12.7. Clovis H. Tigre (b. 1938), director of the programme in Rio Grande do Sul State, developed one of the 4 special state surveillance programmes in Brazil which demonstrated the need for national surveillance. The Rio Grande do Sul programme was exceptionally effective and eventually incorporated the administration of many other vaccines, a forerunner of WHO's later initiative, the Expanded Programme on Immunization.

responsibility for the vaccination campaign, plus 3 epidemiologists, Dr Ciro de Quadros, Dr Nilton Arnt and Dr Eduardo Costa, who had recently graduated from the School of Public Health in Rio de Janeiro. The medical officers were to conduct surveillance after mass vaccination had been completed but the 3 epidemiologists were each to be assigned to the populous states of Paraná, Bahia and Minas Gerais, in which vaccination campaigns had not yet been conducted. There they were to undertake surveillance programmes which might serve as prototypes for other initiatives in infectious disease surveillance. The special surveillance programmes in the 3 states began in March and were extended to a fourth state, Rio Grande do Sul, later in 1969 (Suzart de Carvalho Filho et al., 1970). Approximately 35% of Brazil's population lived in these 4 states.

Although Dr Morais was convinced that surveillance was important, the highest priority for Dr da Silva and the senior smallpox eradication programme staff remained the vaccination campaign, then foundering because of the government's curtailment of funds. There was a reluctance to divert resources to surveillance activities. Only one of the epidemiologists was eventually given a programme vehicle, and then after weeks of discussion. The others were obliged to rely on state health department vehicles, which were rarely available. The only other resources available to them were a driver and a vaccinator, plus whatever help they could recruit from health centres or hospitals. The 3 epidemiologists worked for less than a year before being obliged to resign because of yet another change in the administration of the programme. Subsequently, Dr Arnt and Dr de Quadros were recruited for service with WHO in Africa and Asia, in which they played vital roles in the development of surveillance programmes.

Although the surveillance containment programme that had been set in motion was modest and short-lived, the results proved to be decisive. Through the activities of reporting centres, which would report cases weekly, and through field investigations the epidemiologists soon began to discover large numbers of unreported cases (Azeredo Costa et al.,

Table 12.10. Brazil: susceptibility of residents in affected households, by age and by urban and rural area

Age group (years)	Persons studied						
	Total	With history of smallpox[a]		With vaccination scar[a]		Without history of smallpox and without vaccination scar[a]	
		Number	%	Number	%	Number	%
			A. Urban outbreaks				
⩽4	238	1	0.4	12	5.0	225	94.5
5–14	488	46	9.4	80	16.4	362	74.2
15–29	322	92	28.6	85	26.4	145	45.0
⩾30	335	162	48.4	109	32.5	64	19.1
Total	1 383	301	21.8	286	20.7	796	57.6
			B. Rural outbreaks				
⩽4	318	1	0.3	4	1.3	313	98.4
5–14	576	16	2.8	54	9.4	506	87.8
15–29	416	102	24.5	75	18.0	239	57.5
⩾30	395	218	55.2	94	23.8	83	21.0
Total	1 705	337	19.8	227	13.3	1 141	66.9

[a] Status at time of outbreak.

Table 12.11. Brazil: number of primary cases and attack rate among household contacts, by immunity status, in 27 rural outbreaks of smallpox, 1969

Immunity status	Total number of residents	Number of primary or co-primary cases	Number of household contacts	Number of cases among contacts	Attack rate among contacts (%)
History of smallpox	306	0	306	0	–
Vaccination scar	206	2	204	7	3.4
No vaccination scar and no history of smallpox	1 021	347	674	466	69.1

1971; Arnt & Morris, 1972, Quadros et al., 1972). In an early report, Dr de Quadros and his colleagues documented their findings in the investigation of 27 officially notified cases. By tracing the sources of the outbreaks and through extensive search to identify all cases in each outbreak, they discovered 33 outbreaks in which 1492 cases had occurred. By extrapolation, the studies suggested that the actual number of cases was 50 times greater than the number being reported. In the studies, residents in all the affected households were interviewed to determine if any had previously contracted smallpox and all were examined for vaccination scars (Table 12.10). A uniform reporting form was designed. Although the population under study consisted only of persons residing in houses in which a case had occurred and so were not representative of the community at large, the proportion of residents in affected households who had *ever* been vaccinated was 20% or less. This level of vaccinial immunity was far lower than in any other country of South America.

Epidemiological observations documented the fact that smallpox spread widely among household contacts. Of 674 persons who had neither a history of smallpox nor a vaccination scar, 466 (69%) contracted smallpox (Table 12.11). As expected, a previous attack of smallpox provided total protection, but previous vaccination, even if it had been performed many years earlier, was far more efficacious than had been thought. Only 7 of 204 persons with a vaccination scar developed the disease, and among them it was much milder than among the unvaccinated. The vaccine–efficacy ratio showed levels of protection of 90% irrespective of the interval since previous vaccination (Suzart de Carvalho Filho et al., 1970). These findings served to emphasize the need to give priority to primary vaccination over revaccination.

The outcome of the surveillance programme in Paraná State, conducted by Dr de Quadros, was most dramatic. He began the programme in March, 3 months before the mass vaccination campaign commenced in the state capital. Operating alone in a state

MINISTRY OF HEALTH SMALLPOX ERADICATION CAMPAIGN

EPIDEMIOLOGICAL CASE RECORD
SMALLPOX SURVEILLANCE

IDENTIFICATION DATA

State:
County:
Date of notification | Case No.

Name: | Age | Sex
Address: | City:
How case became known: | Occupation:
☐ Notification ☐ Investigation of another case | Religion:
☐ Other _____

CASE HISTORY AND PRESENT CONDITION

Date of onset of rash:
Hospitalized ☐ Yes ☐ No
Current status of case:
☐ Recovered
☐ Still ill
☐ Died _____ date

Vaccination history:
☐ Never vaccinated ☐ Does not know whether already vaccinated
☐ Vaccinated _____ Year of most recent vaccination (state date if vaccination performed two weeks before onset of rash)
☐ Primary vaccination ☐ Revaccination
Scar present: Yes ☐ No ☐

Was in contact with smallpox patients 7–17 days before the illness:

Name of patient	Age	Sex	Same address	Date of contact	Place of contact: City and county	Place of contact: State
1.			☐ Yes ☐ No			
2.			☐ Yes ☐ No			
3.			☐ Yes ☐ No			
4.			☐ Yes ☐ No			

Journeys outside the town from three weeks prior to the illness up to time of investigation

Dates	Places	Means of transport	Where stayed overnight

LAB

Material collected ☐ No ☐ Yes — Date of collection _____ Results _____

CONCLUSION

Investigator's impression of the case:
☐ Smallpox ☐ Not smallpox ☐ Uncertain

Were contacts vaccinated?
☐ Yes ☐ No No _____

Name of investigator:
Post held:
Signature:
Date of investigation

Plate 12.8. Brazil: standard reporting form for epidemiological investigations. Here translated into English from the original.

with a population of 7 million, he visited health units throughout Paraná to explain the programme and to persuade them to report cases weekly. He investigated every report—which entailed working 7 days a week—and, when outbreaks were discovered, borrowed health staff from clinics and hospitals to perform containment vaccination. By later standards of the Intensified Smallpox Eradication Programme, the containment measures were comparatively simple, but in Paraná they were effective. By August, at a time when the vaccination teams were just completing work in the capital, he had

discovered and contained the last known outbreak. In all, 30 000 persons were vaccinated during containment operations. The mass campaign gradually moved across the state but the staff found no other outbreaks.

Dr da Silva was increasingly impressed by and supportive of the surveillance programme, but at the same time frustrated by a lack of funds and support for the vaccination campaign. Significant progress was being made only in São Paulo State, which financed the programme with state funds. Exasperated, he resigned in July, and for political reasons Dr Morais was replaced in September. Three months later the appointment of the 3 epidemiologists was terminated. Dr da Silva was but the second of 5 persons who were to direct the programme between 1967 and 1972, during which period there were 3 different ministers of health.

Such stability as the programme enjoyed was largely provided by the WHO epidemiologist-statistician, Mr Morris, who, with his Brazilian counterpart, continued to produce the weekly *Boletim* and faithfully recorded the substantial increase in the number of reported cases during 1969. Because of the field investigations, the number of cases in the 4 states tripled between 1968 and 1969, from 1681 to 5370 (Table 12.12). Although this was partially offset by a decline in the number of reported cases elsewhere in Brazil, the net outcome was the highest total number of cases to be recorded in the country since 1962. Because of the *Boletim's* extensive circulation, this dramatic increase in the number of cases (Fig. 12.6) attracted wide attention, including that of the press, the Minister of Health and even the President. Although programme staff repeatedly pointed out that better reporting was the probable cause, there was alarm, and support and resources became much easier to obtain.

Table 12.12. Brazil: number of reported cases of smallpox in 4 states in which special surveillance–containment programmes were conducted, 1968–1969

	1968	1969
Bahia	612	2 140
Minas Gerais	392	1 402
Paraná	218	992
Rio Grande do Sul	459	836
Total	1 681	5 370
Remainder of Brazil	2 691	2 037
Total for Brazil	4 372	7 407

With additional resources from the government and additional vehicles and jet injectors from WHO, the tempo of the

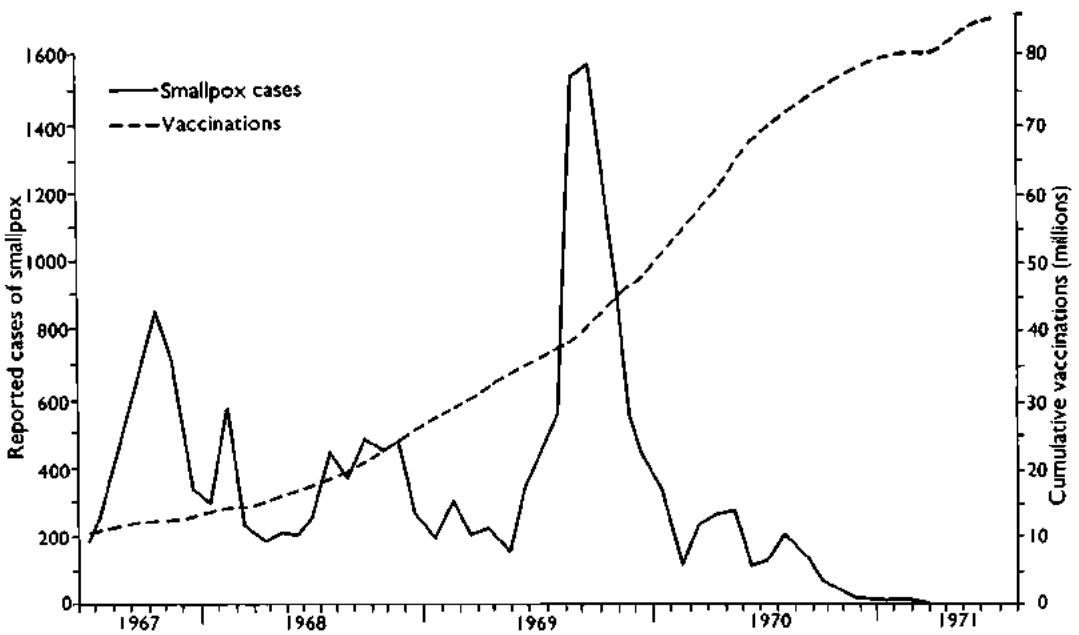

Fig. 12.6. Brazil: reported cases of smallpox and cumulative numbers of vaccinations, by 4-week intervals, 1967–1971.

vaccination campaign rapidly increased (Fig. 12.7). During the last quarter of 1969, 7.3 million persons were vaccinated compared with only 4.2 million during the third quarter. However, with the departure of Dr Morais, Dr da Silva and the 3 epidemiologists, surveillance deteriorated. As was revealed in a survey by a WHO consultant, Dr Paul Wehrle, by February 1970, only 16 of the 27 states and territories had surveillance officers responsible for the investigation and containment of cases. At that time, reports on the situation with regard to smallpox during the month of January were available for only 14 of the 27 states and territories. Even in the states to which officers had been assigned, few notification units were submitting weekly reports. Bahia State, for example, had 200 reporting units, most of which reported monthly rather than weekly. In that state, the consultant found one outbreak that had been reported in November but was not investigated until January. In Pernambuco, only 13 of the 54 reporting posts were found to be currently sending reports. In the other states the situation was not notably better.

CONCLUSION OF THE VACCINATION CAMPAIGN, 1970

The momentum achieved in the vaccination campaign during the last 3 months of 1969 continued into 1970. Programmes were begun in all of the remaining states, the government allocated additional funds, the USA agreed to provide bilateral assistance, and by the end of the year more than 30 million vaccinations had been performed.

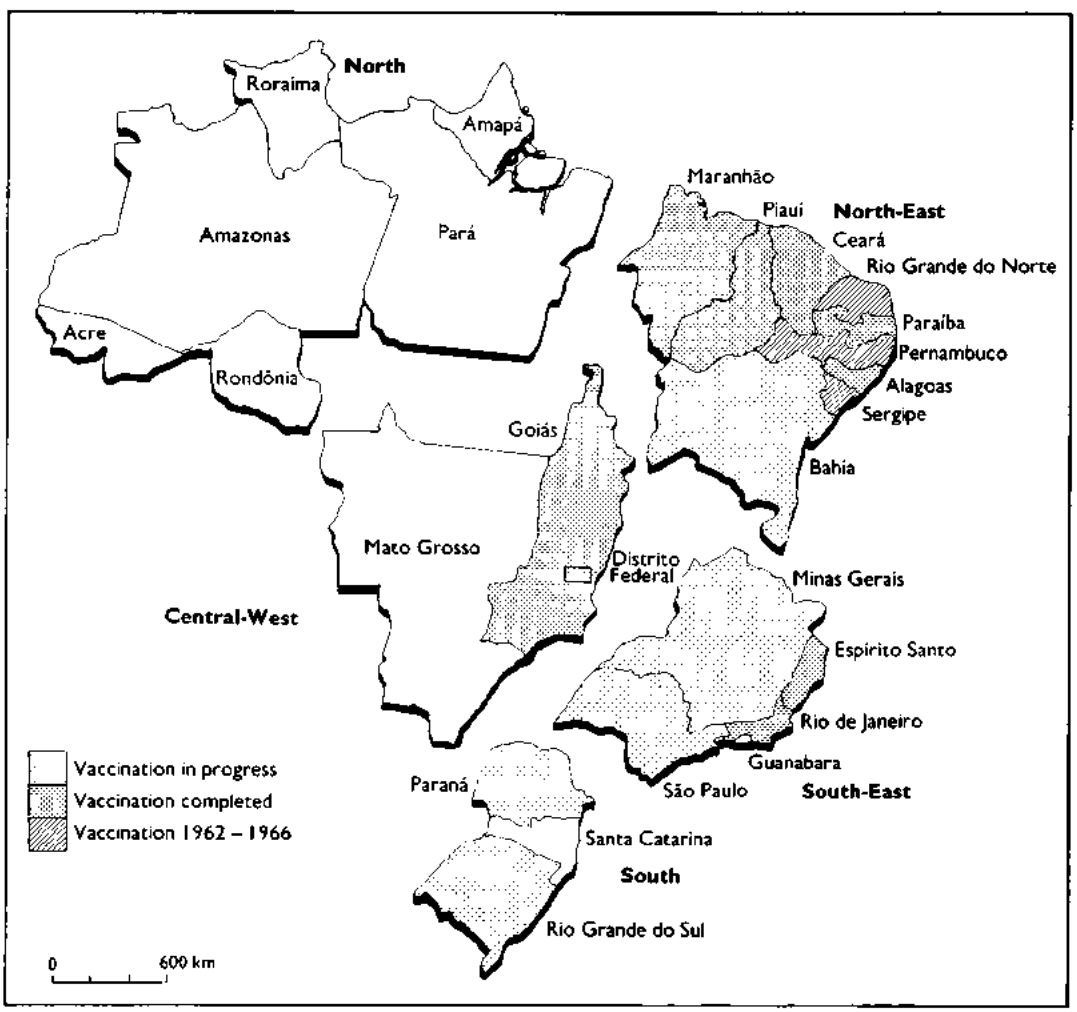

Fig. 12.7. Brazil: status of the smallpox vaccination programme, by region, December 1969.

The Largest Recorded Outbreak during the Brazilian Programme

The largest recorded outbreak in Brazil occurred in the *município* of Utinga, Bahia State, in 1969. A total of 507 cases occurred in a population of 9277 (Azeredo Costa et al., 1971; Azeredo Costa & Morris, 1975). The outbreak was discovered in August, when a newly created surveillance unit in Bahia investigated a single reported case in the *município* of Bom Jesus da Lapa, 300 kilometres south-west of Utinga. The patient, a resident of Utinga, was already ill when she arrived in Bom Jesus da Lapa. The team immediately went to Utinga and discovered an epidemic which had been in progress since February. No cases had been notified by the local authorities. A house-to-house search in the city revealed 246 cases in a population of 2200. Cases occurred also in the surrounding rural areas, in one of which 154 of the 505 residents (30.5%) had contracted smallpox.

Results of a Survey in 104 Households with Smallpox in Utinga City
(Azeredo Costa & Morris, 1975)

Age group (years)	*Number of residents*	*Number with history of smallpox*	*Number with vaccination scar*	*Number fully susceptible to smallpox*	*Number of cases*
⩽4	103	0	9	94	57
5–14	214	21	32	161	124
15–29	148	55	26	67	50
⩾30	153	75	46	32	15
Total	618	151 (24.4%)	113 (18.3%)	354 (57.3%)	246

A survey of residents of the 104 infected households revealed that about 25% had a history of smallpox; another 18% had a vaccination scar. Of the susceptible individuals, 69% contracted smallpox. No cases occurred among those who had already had smallpox; 4 cases occurred among those with vaccination scars, the years of vaccination being 1938, 1947, 1965 and 1967 respectively. The last 2 were very mild cases with few lesions. The age-adjusted vaccine–efficacy ratio was calculated to be 94%.

Ironically, the last of the states to begin a campaign was the state of Guanabara (Fig. 12.8) which, in effect, consisted of the metropolitan area of the city of Rio de Janeiro, the headquarters of the national smallpox eradication programme. The health officer in that state had been one of the least cooperative in reporting cases and had vigorously resisted joining in the vaccination campaign, in part because he considered that the attendant publicity would adversely affect the important tourist industry. Not until October 1970 did he finally agree to permit a selective programme of vaccination at schools, factories and construction sites and among the inhabitants of the slums (*favelas*) and rural areas around the city. A hectic campaign commenced in an effort to reach all of the 1500 schools before the end of the school year in December.

The last cases of smallpox to be discovered in Brazil did not occur in the remote areas of the Amazon basin or in the economically depressed regions of the north-east but in the city of Rio de Janeiro itself, less than 10 kilometres from the national headquarters of the smallpox eradication programme.

The Last Known Cases of Smallpox in Brazil

In November 1970, it was thought that the last cases of smallpox had been detected in Brazil. For more than 12 weeks, no cases were discovered. However, on 1 March 1971, during the last week of the special house-to-house search and vaccination campaign in high-risk areas of the city of Rio de Janeiro, a vaccination team discovered 2 patients with rash and sent them to the isolation hospital. Investigation quickly revealed that 14 cases in all had occurred in 2 groups of adjoining households. The first patient, who had be-

Plate 12.9. Well-organized, intensive publicity campaigns drew large numbers of people to vaccination sites. **A**: Health centre in Cambe, Paraná State, in 1970. **B**: Vaccination post (*posto de vacinação*) in a commercial centre in Goiás State in 1969.

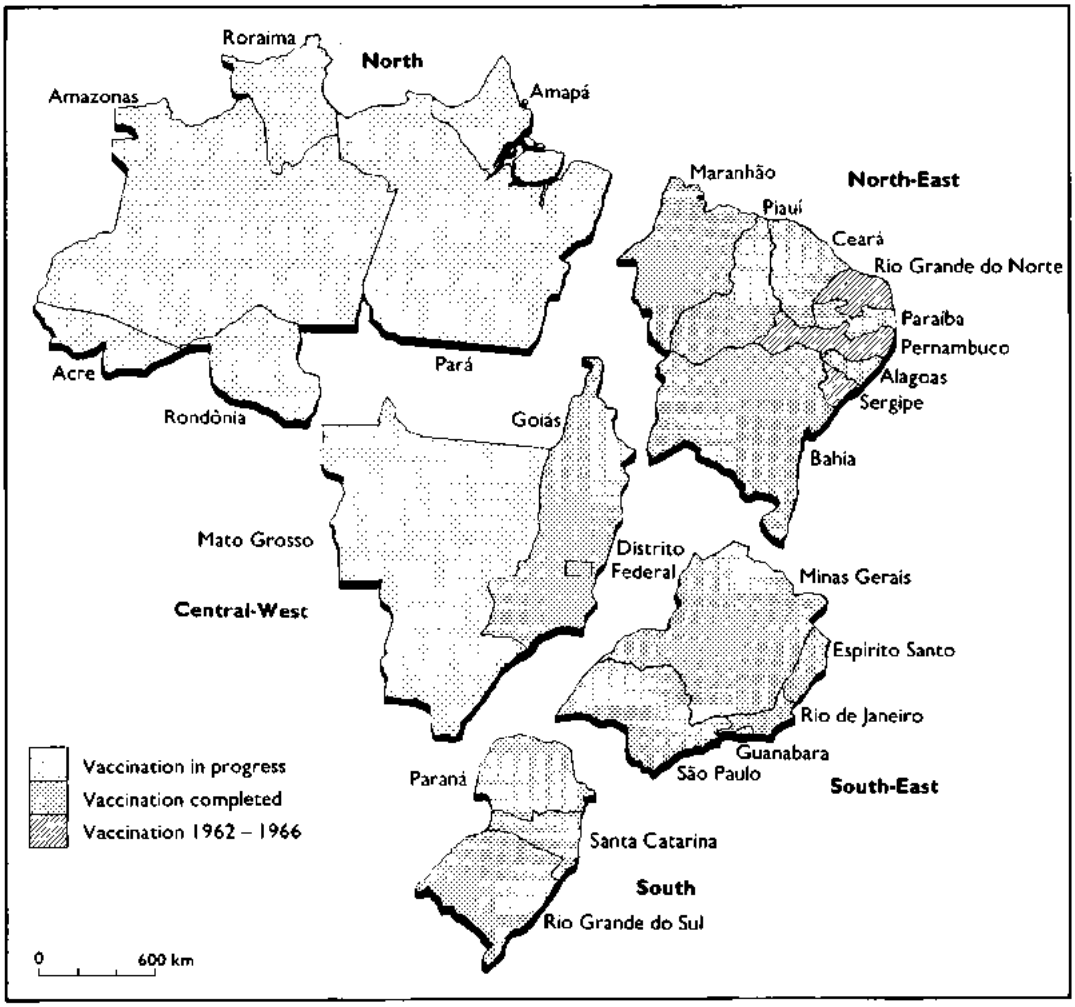

Fig. 12.8. Brazil: status of the smallpox vaccination programme, by region, December 1970

come ill on 22 December 1970, had been displaced from a previously infected area of the city in which many houses had been demolished. Between December 1970 and March 1971, the summer period of seasonally low incidence, smallpox spread slowly.

Intensive search and containment measures were conducted throughout the community. Two additional cases occurred in this area, both of whom were in the incubation period when vaccinated. They were not the last cases, however. The Rio de Janeiro isolation hospital served no better as an isolation facility than did such institutions in most other parts of the world. Three more cases occurred among already hospitalized patients. The third, detected on 19 April, was the last case in the Americas.

Expansion of the Reporting Network, 1970–1971

Although the rudimentary surveillance system had been temporarily strengthened by the addition of the 4 epidemiological units in 1969, few suspected cases were investigated or outbreaks contained until late in 1970. The inadequacy of the system until 1971 is apparent from the data presented in Table 12.13.

During 1970, epidemiological surveillance units began to be established throughout Brazil. Each was under the direction of a physician-epidemiologist who had been specially trained by national programme staff. The units were charged with the following responsibilities:

(1) To establish a network of reporting

Table 12.13. Brazil: number of reported and suspected cases of smallpox and proportion investigated by programme staff, 1967–1973

Year	Number of reported cases	Number of suspected cases	Total	Number investigated by programme staff	% of reports investigated
1967	4 514	0	4 514	230	5
1968	4 372	0	4 372	258	6
1969[a]	2 037	56	2 093	191	9
1970	1 771	296	2 067	412	20
1971	19	450	469	463	99
1972	0	718	718	718	100
1973	0	131	131	131	100

[a] Excludes the states of Paraná, Minas Gerais, Bahia and Rio Grande do Sul, in which special programmes of investigation were conducted (see text).

centres which would report weekly, on a standard form, the presence or absence of suspected cases of smallpox. Each health post would serve as a reporting centre, and in the absence of such a post in a *município*, a responsible official would be asked to provide the requisite information.

(2) To establish and maintain contact with hospitals, physicians, schools, community leaders and any other persons who might be aware of the existence of possible smallpox cases.

(3) To investigate immediately all suspected cases and to undertake the necessary epidemiological and laboratory investigations.

By the end of 1970, surveillance units had been established in 18 states and territories; 2665 reporting centres were in operation.

Meanwhile, smallpox staff joined malaria teams to conduct a systematic programme of search and vaccination throughout the extensive Amazon basin. Five months of work were required, from September 1970 to January 1971; however, no cases of smallpox were detected. Independently, a team of physicians from the International Committee of the Red Cross contacted 20 of 36 Indian tribes in the Amazon basin and reported that they, too, had found no cases among the 4500 individuals whom they examined (*Wkly epidem. rec.*, 1971a).

From 1971 to 1973, Brazil's first national system for disease reporting gradually matured (Table 12.14) under the direction of the last and one of the most able of Brazil's programme directors, Dr Claudio do Amaral, who was later to serve with the WHO smallpox eradication programme in Ethiopia. The number of reporting centres grew from 3243 in 1971 to 6381 in 1973; 444 suspected cases were investigated during 1971 and 718 cases during 1972. Laboratory specimens to confirm diagnosis were obtained from nearly three-quarters of all cases and examined in laboratories in Brazil and the USA (Noble et al., 1970; Schatzmayr & Mesquita, 1970). The systematic vaccination campaign concluded in 1971 with the programme in the Amazon basin and with the revaccination of the population of several states (Pernambuco, Rio Grande do Norte, Alagoas and Piauí) which had been vaccinated during the period 1962–1966 but not subsequently.

In 1972, a national assessment was undertaken during which 778 719 persons in 451 different localities were examined to determine what proportion of their populations bore vaccination scars (WHO/SE/73.51, Amaral et al.). The results are shown in Table 12.15.

The total of 80% with vaccination scars was impressive considering that programmes in some states had concluded as long as 4 years earlier. When the results were examined by state, at least 70% of the population were found to have vaccination scars in all states except Bahia and Ceará, in which the proportions were 59% and 56% respectively.

NUMBERS OF REPORTED CASES AND DEATHS, 1968–1969

Because of the work of the surveillance officers, data are available for 1968–1969 regarding the age and sex distribution of cases, and the case-fatality rates at different ages (Suzart de Carvalho Filho et al., 1970) (Table 12.16).

Nearly three-quarters of all cases (72.6%) occurred among persons under 15 years of age. Among the 9854 cases, only 75 died—a case-fatality rate of just 0.8%, characteristic of

L. MORRIS

Plate 12.10. In 1970, state surveillance units were established throughout Brazil to improve the reporting and investigation of suspected cases. The provision of uniforms, an important fringe benefit, also served to enhance morale.

variola minor. However, among infants under 3 months of age, the case-fatality rate was 16.7% and among those aged between 3 months and 1 year it was 2.0%—more than twice that observed in most other age groups.

RESOURCES EMPLOYED

Data on national expenditures for the campaign are available only for the period 1966–1971. In all, the government of Brazil spent the equivalent of US$4 506 369 from its own budget. The World Health Organization and the Pan American Health Organization expended US$1 763 780 during the same period, primarily for advisers, vehicles, jet injectors, and vaccine and vaccine production equipment, and the sum of US$892 195 was made available by the United States government. Expenditures by state governments are not included in these figures; in São Paulo they were considerable. Additional costs—far lower than these—were incurred during the subsequent 2 years during which the pro-

BY COURTESY OF C. DO AMARAL

Plate 12.11. Claudio do Amaral (b. 1934) speaking at the inauguration of the Maranhão State programme, 1969. With him is the Governor, José Sarney, who became President of Brazil in 1985. After 3 years' service in organizing state vaccination campaigns, do Amaral became the national programme director and developed Brazil's morbidity reporting system.

Table 12.14. Brazil: number of reporting centres, 1971–1973

States and territories	Number of localities	Total number of centres		
		1971	1972	1973
North				
Rondônia	2	1	25	25
Acre	7	1	8	8
Amazonas	44	1	36	42
Roraima	2	1	10	10
Pará	83	1	76	82
Amapá	5	1	10	10
North-east				
Maranhão	129	142	149	151
Piauí	114	140	121	121
Ceará	142	150	161	161
Rio Grande de Norte	150	130	180	180
Paraiba	171	100	159	159
Pernambuco	164	135	194	195
Alagoas	94	96	96	96
Fernando de Noronha	1	1	1	1
Sergipe	74	80	80	80
Bahia	336	214	271	271
South-east				
Minas Gerais	722	288	495	511
Espírito Santo	53	83	84	87
Rio de Janeiro	63	71	86	91
Guanabara	1	23	35	36
São Paulo	571	584	2 710	2 962
South				
Paraná	288	318	317	317
Santa Catarina	197	188	204	204
Rio Grande do Sul	232	227	236	245
Central-west				
Mato Grosso	84	34	93	96
Goiás	221	222	227	227
Distrito Federal	1	11	11	13
Brazil, total	3 951	3 243	6 075	6 381

Table 12.15. Brazil: results of national assessment of vaccinial immunity, 1972

Age group (years)	Number of persons examined	Number with scar	Number without scar	% with scar
<1	17 667	5 040	12 627	29
1–4	77 200	47 377	29 823	61
5–14	338 549	283 054	55 495	84
15–44	295 479	251 066	44 413	85
⩾45	49 824	37 011	12 813	74
Total	778 719	623 548	155 171	80

Table 12.16. Brazil: age distribution of reported cases of and deaths from smallpox, and case-fatality rates, 1968–1969[a]

Age group	Number of cases (%)	Number of deaths	Case-fatality rate (%)
<3 months	84 (1)	14	16.7
3 months–1 year	303 (3)	6	2.0
1–4 years	2 322 (24)	17	0.7
5–14 years	4 389 (45)	8	0.2
15–29 years	1 891 (19)	15	0.8
30–44 years	516 (5)	3	0.6
⩾45 years	276 (3)	4	1.5
Unknown	73 –	8	–
Total	9 854 (100)	75	0.8

[a] Details are not available for 1925 other cases reported during this period.

Table 12.17. Brazil: expenditure in the programme, by source (US$)

Year	National budget	WHO and PAHO assistance	United States assistance	Total
1966	27 036	152 626	-	179 662
1967	647 935	328 295	-	976 230
1968	928 617	481 024	-	1 409 641
1969	1 273 003	382 059	-	1 655 062
1970	1 355 117	243 611	493 891	2 092 619
1971	274 661	176 165	398 304	849 130
Total	4 506 369	1 763 780	892 195	7 162 344

Table 12.18. Brazil: numbers of national personnel, vehicles and jet injectors in the programme, 1968–1971 (as at 31 December each year)

	1968	1969	1970	1971
Personnel:[a]				
Physicians	18	14	14	1
Evaluators	28	64	77	66
Supervisors and vaccinators	729	616	594	308
Drivers	170	172	165	90
Other	87	78	77	86
Total	1 032	944	927	551
Vehicles	178	217	230	-
Jet injectors	219	290	332	-

[a] Excluding state employees.

gramme conducted a variety of search activities to ensure that eradication had been achieved. The national and international expenditures from 1966 to the end of 1971, when transmission was interrupted, thus amounted to US$7 162 344 overall or about US$0.077 per head of population (Table 12.17).

Information regarding the number and category of national personnel employed in the programme as well as the numbers of vehicles and jet injectors was compiled at the end of December each year from 1968 to 1971 (Table 12.18).

SMALLPOX VACCINE PRODUCTION

The development and expansion of facilities for the production of smallpox vaccine in Brazil proved to be a most difficult and frustrating problem. Indeed, the Brazilian programme was unique in that it was possible to interrupt transmission despite the use of vaccines which rarely met accepted standards of potency and stability, and which often contained pathogenic bacteria. The success of the programme testified to a generally well-managed systematic vaccination campaign and vaccine standards that tolerated a substantial margin of error.

In 1967, it had been apparent that large supplies of freeze-dried vaccine would be required for the systematic vaccination campaign in Brazil, as well as additional quantities for Argentina, Bolivia, Colombia, Ecuador, Paraguay, Peru and Venezuela, in each of which an extensive vaccination campaign was planned. When the programme began, freeze-dried vaccine was being produced in a number of South American countries (Table 12.19).

In 1966, little of the vaccine produced by most laboratories met accepted standards of potency and stability, and most of the laboratories were drying the vaccine in containers of 100 or more doses. Since freeze-dried vaccine, after reconstitution, was as thermolabile as liquid vaccine, it should have been used only on the day it was reconstituted. The result was that either significant quantities were wasted or, if the vaccine was kept for several days after being reconstituted, it suffered a considerable loss of potency.

The Connaught Laboratories agreed to test batches of vaccine regularly and to assist laboratories through consultant visits and training, locally and in Canada. Equipment and assistance were eventually provided by PAHO to laboratories in Argentina, Brazil, Chile, Colombia, Cuba, Ecuador, Mexico, Peru, Uruguay and Venezuela. Support was given to countries that requested it, thus accounting for the allocation of resources

Table 12.19. South America: reported production of freeze-dried vaccine, 1966–1972 (thousands of doses)[a]

Country	1966	1967	1968	1969	1970	1971	1972
Argentina	0	560	14 945	21 428	44 350	12 219	17 456
Bolivia	1 800	400	0	230	235	0	0
Brazil	9 386	31 332	49 483	61 000	72 298	44 727	29 387
Chile	37	693	1 962	3 950	721	500	2 583
Colombia	2 535	4 505	7 992	7 587	10 800	4 000	4 008
Ecuador	2 020	1 560	0	0	1 800	2 400	1 017
Peru	1 033	2 220	5 849	6 527	6 228	5 228	5 850
Venezuela	747	624	0	0	0	0	301
Total	17 558	41 894	80 231	100 722	136 432	69 074	60 602

[a] From Rodrigues (1975).

even to countries at little risk such as Chile, Cuba and Mexico. It would have been more logical to concentrate efforts in Brazil, whose laboratories were experiencing the greatest problems. The Connaught consultants, however, were directed to travel throughout the continent assisting laboratories in numerous countries. Less than one-third of their time was spent at the principal vaccine production centre in Brazil, the Oswaldo Cruz Institute, which experienced constant difficulties and never did succeed in producing a consistently satisfactory product.

Data regarding the quality of vaccines produced by the different laboratories in the Americas are regrettably scanty. Each laboratory was supposed to test its own vaccine and to send samples of each batch to the Connaught Laboratories until it was certain that a satisfactory vaccine was being produced consistently; thereafter, 2 batches were to be sent for testing every 3 months. Comparatively few samples, however, were submitted for independent testing. From an assessment of the limited data available from the Connaught Laboratories and from reports of visits by consultants, it would appear that the vaccine produced in Argentina, Chile and Colombia consistently met WHO standards, while that produced in Ecuador and Peru sometimes failed to meet standards of stability—i.e., when the vaccine was incubated at 37 °C for 1 month, its titre fell below an accepted minimum standard. The Brazilian laboratories seldom produced batches of vaccine which met international standards (see Chapter 11). Many batches were low in initial potency and most failed to meet stability standards. Vaccine for use in Brazil's systematic vaccination programme was produced exclusively at the Oswaldo Cruz Institute. Vaccine from the other laboratories was distributed to health centres and hospitals for what was termed "maintenance vaccination."

At the Oswaldo Cruz Institute, much of the vaccinia virus was grown in embryonated hens' eggs. Experience elsewhere had shown that, for technical reasons which are still unexplained, virus harvested from this source rarely met accepted standards of stability. In the endemic countries, none of the laboratories except the Oswaldo Cruz Institute and Brazil's vaccine production centre in Pôrto Alegre used this method of production. In addition to being unstable, many of the batches from the Oswaldo Cruz Institute failed to meet minimum standards of potency. However, the vaccine which the Institute produced on calves (about half of its production) was little better, in terms either of potency or of stability, and most batches were found to be contaminated with numbers of pathogenic bacteria (coagulase-positive staphylococci and non-haemolytic streptococci). Of 43 batches of Oswaldo Cruz vaccine tested by the Connaught Laboratories as late as 1970, 35 failed to meet accepted stability standards, and 13 of the 43 batches were below minimum standards of potency. In January 1970, 15 vials of Brazilian vaccine were collected from the field and tested; only 2 met the accepted standards of potency. Moreover, as a WHO consultant noted at that time, the vaccine was not labelled as to origin or lot number and no expiry date was stamped on the containers.

Vaccine production units at Recife and Pôrto Alegre had equally poor records, and although WHO consultants recommended that they should be closed, they continued to produce vaccine. Not until late in 1970, near the end of the programme, did fully satisfactory vaccine become available. At that time, the Butantan Institute in São Paulo began producing a consistently satisfactory vaccine from virus harvested from calves.

Despite the poor vaccine, assessment teams usually found that take rates for primary

Table 12.20. Brazil: number of doses of vaccine produced and number of vaccinations performed, 1967–1972 (millions)

	1967	1968	1969	1970	1971	1972
Doses of vaccine produced	31.3	49.4	61.0	72.3	44.7	29.3
Vaccinations performed:						
"Attack phase"	6.6	12.2	20.9	31.6	12.0	0
"Routine maintenance"	11.4	9.2	5.0	5.7	6.0	13.9
Total	18.0	21.4	25.9	37.3	18.0	13.9

vaccinations were above 90%. However, to achieve a high proportion of successful takes, it was necessary to ensure that the vaccine was kept refrigerated until the time of use. When refrigeration was available, the take rates were generally satisfactory, but in more remote areas that lacked such facilities, they were not. The results of assessment in Espírito Santo State illustrate this: take rates of 98% were obtained among those vaccinated in urban areas, but in the more remote areas in which refrigeration was a problem, the rates were 88–93%. In other parts of the world, where fully potent and stable vaccine was available, take rates of 98% or higher were the rule, even when vaccine was kept at ambient temperatures for a month or longer.

The large quantities of vaccine reported to have been produced in Brazil (Table 12.20) far exceeded the amounts required for the numbers of vaccinations performed. Yet, despite the large volume of production reported, available vaccine supplies so frequently dropped to critical levels in Brazil that reserve supplies were requested from and donated by Argentina in 1970. The explanation of this paradox lies, in part, in the vagaries of Brazilian laboratories in reporting vaccine production. Virtually all other laboratories reported the numbers of doses produced in terms of 1 dose being equivalent to 0.01 ml of reconstituted vaccine. An ampoule containing the standard amount of 0.2 ml or 0.25 ml was reported as 20 or 25 doses. When the conventional scarification technique had been used, this correspondence between the number of doses and the size of the ampoule was approximately correct, but with the introduction of the jet injector and the bifurcated needle many more persons could be vaccinated with the same amount of vaccine. Notwithstanding this development, producers elsewhere continued to report production on the basis of 0.01 ml of reconstituted vaccine being equivalent to 1 dose. The Oswaldo Cruz Institute, however, produced vaccine in ampoules which, when reconstituted, contained 0.35 ml and 1.0 ml and which were designated, respectively, as 100 and 400 doses. Similar practices were followed in other Brazilian laboratories. Not only was reported production inflated by a factor of 3–4 compared with that of other laboratories, but wastage in the field was greater because of the larger ampoules.

The extensive use of a consistently inferior vaccine in Brazil throughout most of the period of the programme was compensated for by the closely supervised vaccination campaign. Had vaccines of comparable quality been employed in most other programmes, the transmission of smallpox would not have been interrupted.

CONCLUSIONS

Eradication was finally achieved in Brazil, and in South America as a whole, in April 1971, nearly 5 years after the promulgation of the federal decree of 31 August 1966 which set the programme in motion in Brazil. However, as in many other countries, the progress achieved by the programme was erratic and the chances of success were in doubt as late as 1970.

Several factors may be seen, in retrospect, to have been essential to the achievement of eradication. In the initial stages, Dr da Silva's organizational talents, tested during years of work in malaria eradication, served to establish an effective administrative structure. Thereafter, observations made during field investigation, assessment of vaccine coverage and surveillance altered strategy and provided a necessary stimulus to government at critical moments. At an early stage, field investigation of an outbreak in a town whose inhabitants were said to have been well vaccinated dramatically pointed up the need for routine assessment of vaccination coverage and take rates. An assessment programme,

The Precarious Status of the Programme in Brazil, February 1970

Extracts from a letter from D. A. Henderson to Dr Charles Williams, Deputy Director of PAHO, dated 10 February 1970:

"It seems quite clear that the situation is not good. Both Drs Candau [Director-General of WHO] and Horwitz [Director of PAHO] were very concerned and had communicated this to me during the EB [WHO Executive Board meeting, held in January]...

"The visit of Dr Wehrle [a WHO consultant] originally had been thought of as an effort to strengthen surveillance as, from the reports, it seemed like one additional modest push in the right direction could put the programme over the top... however, surveillance, such as it is, is collapsing along with a good many other things; much had been said about the development of the network of reporting centres but, in fact, very little had been done and even in those states where it was said to be well-established, this was anything but the case.

"Candidly, I'm afraid that WHO is in no small way at fault. Despite Brazil having been recognized as the No. 1 problem, from the beginning, Connaught Laboratories' consultants have been dispatched from Cuba to Mexico to Peru with an occasional brief stop at the one laboratory which supplies 80–90% of all vaccine to the one endemic country...Parenthetically, the Brazilian laboratories are now the *only* producing laboratories in endemic countries manufacturing sub-standard vaccine. Money has been directed to smallpox projects in any number of countries (most recently Venezuela!) when, in fact, the real need is Brazil plus the need to keep a watchful eye on Paraguay and northern Argentina. Now even the man for this latter function has been terminated, so I have just learned...

"I would hope we could chart some alternative future course at the earliest possible time ...some sort of reasonably high level discussions in Brazil should be arranged at the earliest possible time."

using a sample survey technique, was quickly developed; this evolved into one of the most effective and thorough of any smallpox eradication programme.

The weekly surveillance bulletin (the *Boletim semanal*), launched in May 1967, documented the programme's progress or setbacks for staff at all levels and communicated information on new developments and procedures to everyone concerned. When a perceptive health secretary assigned 3 surveillance officers for surveillance–containment functions and these workers promptly discovered an additional 50 cases for each case investigated, the weekly bulletin broadcast the news of what seemed to be an alarming epidemic. The press, the Minister of Health and even the President took a new interest in the programme. By the middle of 1970, it achieved its full momentum.

Whether transmission could have been interrupted without the extensive vaccination programme but with effective surveillance–containment measures is an unanswerable question. Because the disease occurred only in the mild variola minor form, there was less of a stimulus for vaccination, and thus vaccinial immunity in Brazil in 1967 was probably among the lowest in the endemic countries. Transmission was successfully interrupted in Paraná State by surveillance–containment measures alone, but Paraná was one of the more prosperous states with a more extensive health infrastructure than those in the north-east and in the Amazon area.

Whatever the shortcomings of the programme, eradication was achieved in somewhat less than 5 years in a population of nearly 100 million people. In the course of the programme, a large cadre of young health staff obtained practical training and experience in epidemiology, which they were subsequently to apply to other health problems during service in Brazil and in international health organizations. The household probability survey, used in assessment, was later adapted for similar use in other programmes, ranging from family planning to poliomyelitis; and the weekly smallpox surveillance bulletin has since become Brazil's weekly communicable disease report.

CHAPTER 13

INDONESIA

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INTRODUCTION

In 1967, smallpox was endemic in 5 Asian countries, whose total population amounted to 769 million. Four of these countries—Afghanistan, India, Nepal and Pakistan—were contiguous, sharing long borders, which travellers (including people infected with smallpox) crossed with relative freedom. However, the fifth country, Indonesia (population, 112 million), lay some 2000 kilometres south-east of the nearest endemic area on the continent—East Pakistan (after 1970, Bangladesh). Comparatively few people travelled between Indonesia and the other 4 countries. Thus, it seemed logical and opportune to concentrate resources and energies initially in Indonesia in the expectation that on becoming free of smallpox, the country would not be seriously threatened by importations (*Wkly epidem. rec.*, 1969a). WHO resources committed to Indonesia could then be shifted to other programmes in Asia. The fact that smallpox transmission had once been interrupted in Indonesia, immediately before the Second World War, added strength to the belief that the objective could be attained.

As had been hoped, Indonesia was the first of the 5 Asian countries to become free of smallpox. The programme began there in June 1968; the last known case occurred little more than 3½ years later, on 23 January 1972. The achievement of eradication so quickly in such a large and populous country was both a surprise and a stimulus (and to some degree an embarrassment) to health staff in Bangladesh, India and Pakistan, whose programmes had by then been in progress for a decade. That this feat had been accomplished with little more than US$1 million in international assistance made it even more notable.

Success was not easily achieved in the Indonesian programme. Smallpox was tenacious and spread readily even among populations with exceptionally high levels of vaccinial immunity—a marked contrast to the

behaviour of the disease in most endemic countries of Africa and the Americas. Full credit for the achievement is due to an imaginative group of Indonesian and WHO staff, who conceived and evolved effective strategies that were later adapted for use in other parts of the world and proved vital to the interruption of smallpox transmission in the Indian subcontinent. Among Indonesia's contributions to global eradication were the concept of a special programme involving a village-by-village search for cases, the introduction of a reward system for anyone reporting a case of smallpox and the development of the widely used WHO smallpox recognition card (see Chapter 10, Plates 10.29, 10.30).

A number of papers were prepared describing selected aspects of the Indonesian programme, although a book would have been warranted to recount the whole gamut of activities. There was little time available to attempt a detailed narration, however. When eradication was certified in 1973, experienced staff were urgently needed in other countries; key Indonesian staff and the WHO advisers who had been assigned there responded promptly and, in so doing, contributed to the record of achievement compiled in India, Bangladesh and Ethiopia.

THE DECISION TO BEGIN THE PROGRAMME

Originally it had been hoped that the campaign in Indonesia might begin during the first year of the Intensified Smallpox Eradication Programme but its start was delayed until June 1968. In part, this stemmed from doubt and inertia in the WHO Regional Office for South-East Asia in New Delhi, India. The then Regional Director believed that the health resources in the countries of the region were too inadequate to permit eradication to be realized. He frankly and publicly stated his view that the World Health Assembly's decision to undertake global eradication was ill-advised, and consequently offered little support to the programme. Likewise, the Regional Adviser for Communicable Diseases, the senior technical officer, took little interest. A memorandum of 10 October 1967 from Henderson to his superior in WHO Headquarters, Dr Karel Raška, the Director of the Division of Communicable Diseases, summarized the situation prevailing during much of that year:

"In December [1966] and April [1967], the considerable importance of an early visit to Indonesia to assess Government interest and capability to undertake [smallpox eradication] had been agreed by [the Regional Adviser for Communicable Diseases] and myself. No visit has yet been undertaken and none is contemplated until possibly November. In fact, I gather there was no correspondence with Indonesia on the question of [eradication] until July ... No solutions are proposed; no possible courses of action are outlined."

Subordinate to the regional adviser and ostensibly responsible for providing assistance to countries in developing smallpox eradication programmes was a 2-man intercountry advisory team for epidemiology whose duties then encompassed a range of different activities. During his visit to New Delhi, Henderson had met the team, which had exhibited both an interest and a desire to proceed rapidly in the development of WHO smallpox eradication programmes. Subsequent communication with them by mail proved difficult. All correspondence relating to smallpox eradication between WHO Headquarters and the regional office, as well as between the countries and the regional office, was routed first to the regional adviser. Seldom was it passed to the intercountry team. By the end of November 1967, the intercountry team had been permitted to make only two brief visits, to Afghanistan and Nepal, the only countries in the region in which WHO-supported smallpox eradication programmes were then in progress. In the autumn of 1967, one of the team's members, Dr Jacobus Keja, prepared a draft plan of operations for Indonesia but was denied permission to visit the country to discuss the plan.

The lack of activity in the South-East Asia Region and its failure to obligate smallpox eradication funds allotted for the calendar year led to important financial ramifications in the global programme as a whole. When the budget for smallpox eradication for 1967 had been approved by the Nineteenth World Health Assembly, several countries had expressed the view that an allotment of US$2.4 million for the first year was too large and proposed instead that a sum of US$1 million should be provided (see Chapter 9). The larger allocation was eventually agreed on, but only after assurances had been given by the Director-General that the full amount was needed and could be spent. In the American and Eastern Mediterranean Re-

gions, activities were progressing sufficiently well to ensure that the funds allotted to them would be obligated. However, US$806 000 had been assigned to the South-East Asia Region and little of it had been spent. If these funds were not obligated by the end of the year, not only would they be lost to the programme, but the possibility of questions arising at the next World Health Assembly could be foreseen, conceivably resulting in reductions in subsequent budgets for smallpox eradication. Because of this problem, the Regional Director finally agreed, in November 1967, that the intercountry team should discontinue its other activities and assume primary responsibility for smallpox eradication under a higher-level regional office official, the Assistant Director for Health Services. With this administrative change, the development of a programme in the region became feasible.

Three other events occurred during the autumn of 1967 which were to alter significantly the possibilities for eradication in the South-East Asia Region and in Indonesia in particular. A new WHO Regional Director, Dr Herat Gunaratne, was nominated in September 1967 and took office in February 1968. As President of the Twentieth World Health Assembly, in May 1967, Dr Gunaratne (a former Director-General of Health Services in the smallpox-free country of Sri Lanka) had stated categorically that the eradication of smallpox was wholly achievable, that it was simply a matter of will and determination. As testimony to this belief, he offered his own considerable enthusiasm and support for the programme.

The second event was the appointment in November 1967 of Dr Julie Sulianti Saroso to the post of Director-General for the Control and Prevention of Communicable Diseases in the Indonesian Ministry of Health. This decisive and energetic woman was determined to revivify a discouraged and listless health staff who had received little pay for more than 4 years because of a decision by the previous government that health care costs should be borne primarily by private individuals. Although the health staff were expected to supplement meagre salaries through charges for their services, few were successful in obtaining even subsistence wages. Dr Sulianti promptly asked for help from WHO. The regional office decided that Dr Keja should visit Indonesia en route to an intercountry seminar on smallpox, due to begin in Bangkok on 11 December. He arrived in Jakarta on 7 December 1967.

The third event was the development of epidemic smallpox, beginning in August 1967 with an outbreak in the capital city, Jakarta. By November, more than 50 cases a week were being reported (Fig. 13.1).

With Dr Sulianti, Dr Keja at once decided to carry out a sample survey of the city to

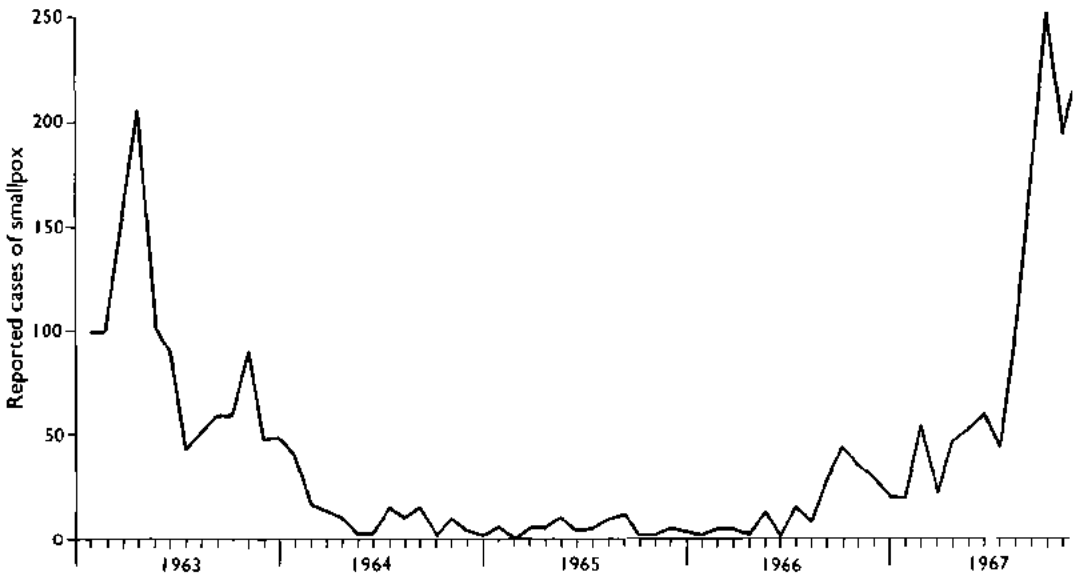


Fig. 13.1. Jakarta Municipality: number of reported cases of smallpox, by 4-week intervals, 1963–1967.

BY COURTESY OF N. KUMARA RAI

Plate 13.1. Several national and intercountry seminars on smallpox eradication were held in Indonesia. At the concluding seminar, in September 1972, Julie Sulianti Saroso, Director-General for the Control and Prevention of Communicable Diseases, presented an award to Nyoman Kumara Rai, who had directed the Indonesian Programme since April. Standing behind the Director-General are 2 WHO advisers, G.G.O. Cuboni (*far left*) and W. L. R. Emmet.

assess vaccinial immunity—the first of many such surveys to be conducted during the global programme. For this survey, 20 field staff from the smallpox and malaria programmes were selected and trained. Each examined 200 children for vaccination scars and the facial pockmarks of smallpox in a house-to-house survey beginning from randomly selected points in the city. In only 4 days, the survey had been completed and the results analysed. From the survey and a review of other available data, it was apparent that there were major problems:

(1) Reporting was incomplete. In all, 1265 cases and 413 deaths had been recorded during 1967, but because so many cases were found during the survey the actual number of cases was thought to be at least twice this figure.

(2) The number of vaccinations given was insufficient to sustain immunity. Jakarta Municipality's 49 vaccinators had performed 384 000 vaccinations in 1967, but only 35 295 (9.2%) had been primary vaccinations. In a population of 1.4 million, with a birth rate of 40 per 1000, it was calculated that 56 000 primary vaccinations would be required annually simply to protect newborn infants.

(3) The proportion of successful primary vaccinations was unsatisfactory. Take rates of only 60–80% were observed, a phenomenon attributed to the use of vaccine of lower than acceptable titre as well as unsatisfactory vaccination technique.

However, vaccinial immunity, though still not adequate, was found to be far higher than expected. Vaccination scars were seen in 90% of children aged 5–14 years, in 75% of those aged 1–4 years, and in 45% of infants aged less than 1 year. Nevertheless, the situation was clearly disturbing. Smallpox was spreading rapidly throughout a reasonably well vaccinated urban population; the vaccination campaign was lagging and was further compromised by the use of substandard vaccine; extension of the epidemic into less well vaccinated rural areas was only a matter of time. A programme for smallpox eradication

Table 13.1. Indonesia: population and number and category of administrative units, by island, 1968

Island	Estimated population[a] (thousands)	Administrative units				
		Provinces	Regencies	Municipalities	Subdistricts	Villages
Bali	2 097	1	8	0	50	560
Java	73 224	5	82	24	1 514	21 910
Kalimantan	4 844	4	28	6	376	6 120
Maluku	932	1	4	1	51	1 605
Nusa Tenggara	4 450	2	18	0	154	2 267
Sulawesi	8 358	4	33	4	354	3 838
Sumatra	18 579	8	52	19	669	9 204
West Irian	896	1	9	0	35	892
Total	113 380	26	234	54	3 203	46 396

[a] Population estimates as recorded in 1968. United Nations (1985) data show a total population of 114 798 000 for Indonesia in 1968.

was urgently needed and indeed its development proceeded rapidly.

The above-mentioned WHO intercountry smallpox seminar in Bangkok, which, by lucky timing, took place immediately after the Jakarta survey, provided the opportunity for a draft plan of operations to be finalized. Indonesia's representative, Dr Ignatio Setiady, Director of Communicable Disease Control, met Henderson and Dr Keja, and using the latter's earlier prepared draft, worked out a plan for the programme and estimated the cost involved and the assistance required.

A critical problem, and one that was never really solved, was that of providing Indonesian staff with high enough salaries to permit them to work virtually full time. Vaccinators, for example, were then receiving the equivalent of US$2 a month, which was insufficient to buy food for themselves, let alone for their families. WHO's resources could not deal with the situation in its entirety. Despite this problem, it was apparent from the survey that somehow a large proportion of the population was being vaccinated. With hope rather than confidence that the vaccinators would continue to function, it was agreed that supplementary WHO funds would be provided to a small number of senior Indonesian staff to permit them to carry out full-time supervisory functions; other personnel would necessarily work only part time, and field operations would have to take this into account. WHO also agreed to provide a medical officer and to purchase various items, including 15 vehicles, 135 motor cycles, 1550 bicycles, 23 refrigerators and vaccine production equipment. By the end of December, funds for equipment and supplies had been obligated. Less than a month later, on 24 January 1968, Indonesia's Minister of Health signed a formal agreement with WHO authorizing the programme. Field operations were scheduled to begin in June 1968.

WHO

Plate 13.2. Ignatio F. Setiady (b. 1929), Director of Communicable Disease Control, at the 1967 WHO seminar in Bangkok, Thailand, where plans for the Indonesian programme were worked out.

DEMOGRAPHY AND GEOGRAPHY OF INDONESIA AND ITS HISTORY OF SMALLPOX CONTROL

The country's demographic and geographical features, as well as its remarkable history of smallpox control, were determining factors in the development and progress of the programme.

The Indonesian archipelago, extending over more than 4800 kilometres, consists of

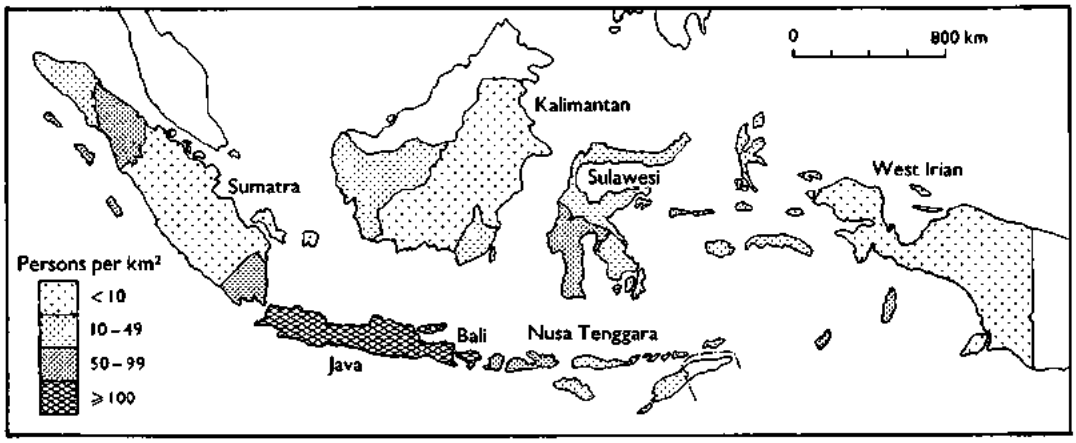


Fig. 13.2. Indonesia: population density, 1968.

some 13 000 islands, of which 3000 are inhabited. In 1968, 66% of the country's 115 million people lived on the densely populated islands of Java and adjacent Bali (Fig. 13.2; Table 13.1). Most of them (83%) lived in localities with 5000 or fewer inhabitants or in rural areas. However, it was estimated that fully 60% of the population could be reached by motorized vehicle, 20% by boat and 20% on foot or by bicycle.

For administrative purposes, Indonesia in 1968 was divided into 26 provinces, which were subdivided into 288 regencies and municipalities (Table 13.2), consisting of 3203 subdistricts. The smallest administrative unit was the village. The size of the population in these administrative divisions varied considerably from one area to another.

Although organized vaccination campaigns in Java dated back to 1856, an extraordinarily effective campaign was begun in the 1920s which was successful in interrupting smallpox transmission as early as 1936 (Table 13.3).

Of the 21 cases recorded between 1937 and 1940, 7 were found to be importations and the others were suspected to be either importations or mistaken diagnoses (Polak, 1968). The Second World War intervened and morbidity reporting ceased. After the war, no cases are known to have occurred in Indonesia until May 1947. The first cases were reported from the Riau Islands, adjacent to Malaysia, in which smallpox was then endemic. Over the next few years, the disease swept eastwards across the western and central islands of the archipelago, 99 016 cases being reported in 1950. However, smallpox did not spread beyond Sulawesi and West Nusa Tenggara to the numerous but more sparsely populated islands to the east—East Nusa Tenggara, Maluku and West Irian (Fig. 13.3).

The methodology employed in the vaccination campaign of the 1920s and 1930s is of interest, since the structure and many of the operational components of the campaign still existed in 1968 (Polak, 1968), although the number of staff had diminished and the

Table 13.2. Indonesia: number and population range of administrative units

Administrative unit	Number	Population range
Province	26	500 000–28 000 000
Regency/municipality	288	50 000–1 000 000
Subdistrict	3 203	5 000–100 000
Village	46 396	< 1 000–10 000

Table 13.3. Indonesia: number of reported cases of smallpox, 1924–1940

Year	Number of cases		
	Total for Indonesia	Java	Other islands
1924	6 717	5 941	776
1925	4 681	4 658	23
1926	855	843	12
1927	766	297	469
1928	298	46	252
1929	614	271	343
1930	419	408	11
1931	176	69	107
1932	562	349	213
1933	57	7	50
1934	9	4	5
1935	43	10	33
1936	80	1	79
1937	1	1	0
1938	12	9	3
1939	2	2	0
1940	6	0	6

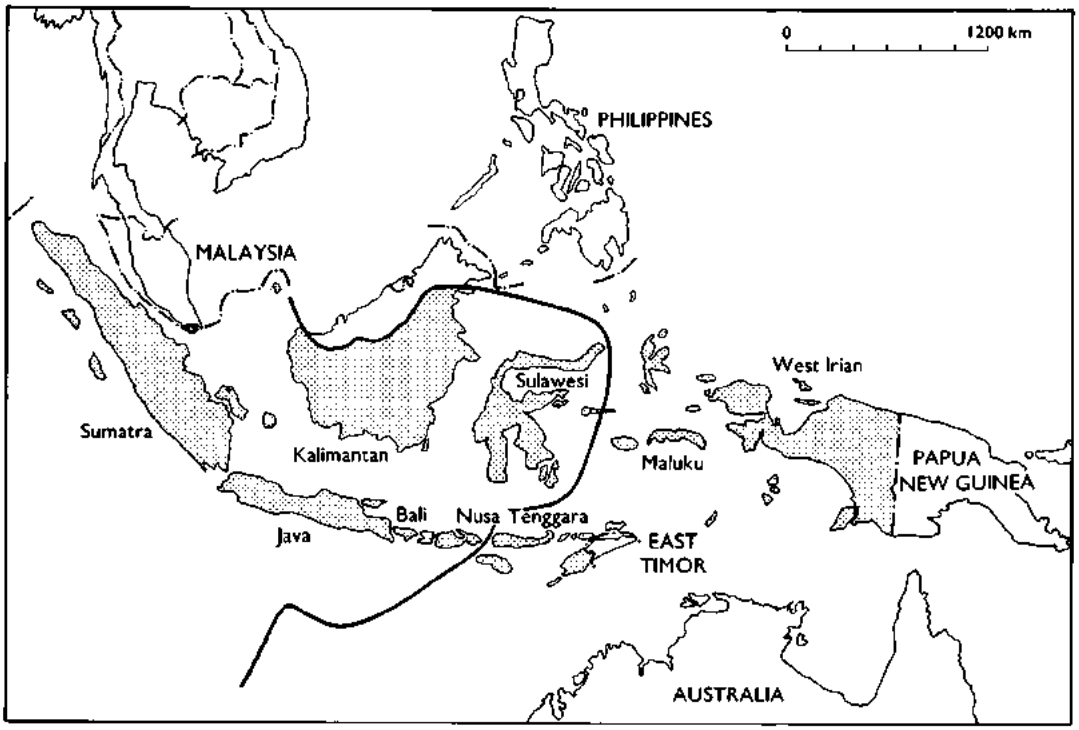


Fig. 13.3. Indonesia and adjacent countries. The heavy line shows the limit of the spread of smallpox after its reintroduction in 1947.

quality of performance was poorer. A trained vaccinator was assigned a vaccination district of about 100 000 persons. Under the supervision of a medical officer who was responsible for several regencies, he travelled by bicycle and on foot through his assigned district on a strictly prescribed schedule. During each 3-month period, he devoted 8 weeks to primary vaccination and 5 weeks to revaccination. Infants were brought to designated collecting points not more than 6 kilometres from their homes and up to 150 were vaccinated daily. In the case of revaccination, up to 500 persons were dealt with each day. When outbreaks occurred, intensive programmes of vaccination were conducted in the areas infected. Most vaccinators used liquid vaccine, produced by the government-owned quasi-independent Lymph Institute in Bandung (Biofarma), which had opened in 1891. In the more remote districts, a remarkably stable, room-dried and vacuum-sealed vaccine was used which had been first produced in 1926 (Otten, 1932).

In the systematic vaccination campaign, resumed after the Second World War, both liquid and room-dried vaccines and eventually some freeze-dried vaccine were used. High inflation rates and the drastic reduction of salaries of government health staff forced vaccinators and other personnel to take additional jobs. Periodic *ad hoc* mass vaccination campaigns were also conducted, financed by local merchants and village organizations. The numbers of vaccinations reported by vaccinators in Java from 1963 to 1967 indicate the extent of activity (Table 13.4).

In all, 15–25% of the population in the different provinces were reported to have been vaccinated annually by the special vaccinators. Of the total number of vaccinations, 10–15% were recorded as primary vaccinations. In addition, vaccinations were performed in local clinics and maternal and child health units; these were not included in the totals but their number was thought to be large. On the basis of this information, it was difficult to guess the probable extent of vaccinial immunity. Not only were the reports of vaccinations performed considered to be suspect, but primary take rates were reported to range from 33% to 88%. Both high and low rates were recorded during the use of each of the 3 forms of vaccine then being produced: liquid, room-dried, and a small quantity of freeze-dried vaccine. Be-

Table 13.4. Java: Estimated population, 1965, and number of reported vaccinations in selected provinces, 1963–1967

Province	Estimated population, 1965 (thousands)	Number of vaccinations (thousands)				
		1963	1964	1965	1966	1967
Central Java	20 225	3 601	3 866	6 188	4 648	7 386
West Java	19 122	2 542	2 106	2 986	3 294	3 545
Jakarta	3 500	634	1 844	103	1 344	469
Jogjakarta	2 462	370	318	637	381	1 059

Table 13.5. Java: proportion of children susceptible to smallpox,[a] by age group; surveys of December 1967–January 1968

Age group (years)	Jakarta	West Java	Central Java	East Java
<1	55%	51%	46%	72%
1–4	25%	27%	7%	23%
5–14	10%	12%	3%	7%
0–14	22%	25%	12%	20%
Number of children examined	4 148	19 069	19 041	18 509

[a] I.e., children who had neither facial pockmarks characteristic of smallpox nor a vaccination scar.

cause refrigeration facilities were limited, low primary take rates with the thermolabile liquid vaccine were understandable. The low take rates with the more stable freeze-dried and room-dried vaccines reflected, in part, the low potency of some batches; moreover, none of the dried vaccine was kept under refrigeration, since the manufacturer claimed that it retained its potency at room temperature for 18 months. Although a few batches attained this degree of stability, most did not.

Special mass vaccination campaigns had been conducted in Jakarta in 1962–1963, in East Java in 1964, in West Java in 1965 and in Central Java beginning in the autumn of 1966. The campaigns were not well supervised or well coordinated and were chronically short of funds to pay vaccinators and to purchase vaccines from the Biofarma laboratory.

Despite the apparently questionable efficacy of the campaign, vaccinial immunity in Java proved to be surprisingly high, although the level of immunity varied widely from one locality to another. Sample cluster surveys, similar to the one conducted by Dr Keja in Jakarta in December 1967, were carried out in January and February 1968 throughout Java. In all, 56 619 children under 15 years of age were surveyed. All the children were examined to determine whether facial pockmarks were present and whether or not they had a vaccination scar. From these studies, an estimate of the level of vaccinial immunity was obtained (Table 13.5), as well as an approximation of the completeness of smallpox notifications.

Less than one-quarter of all the children were considered to be fully susceptible to the disease. Only 807 (1%) had facial pockmarks characteristic of smallpox. Since persons less than 15 years of age constituted approximately half the population and since only a small proportion of those older than 15 were fully susceptible, it was assumed that not more than perhaps 10–15% of the total population were then susceptible to smallpox. Not surprisingly, at that time more than 75% of smallpox cases were reported to be occurring among children under 15 years of age (Table 13.6) and upwards of 80% of cases occurred among those without a vaccination scar.

SMALLPOX INCIDENCE, 1963–1967

National data for smallpox prior to 1963 provide little indication as to the incidence or

Table 13.6. Jakarta and East Java: age distribution of cases of smallpox, 1965–1966

Age group (years)	Jakarta	East Java
<1	13%	11%
1–4	55%	37%
5–14	16%	28%
⩾15	16%	24%
Number of cases	308	4 442

Table 13.7. Indonesia: number of reported cases of smallpox, by province, 1963–1972[a]

Province	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972
Bali	0	0	6	2 652	43	0	0	0	0	0
Java:										
West Java	13 773	2 994	809	1 419	4 518	9 548	11 966	4 490	186	34
Jakarta	1 155	174	99	223	1 504	1 231	392	130	9	0
Jogjakarta	0	0	6	40	34	3	2	0	0	0
Central Java	1 196	1 509	3 289	2 727	2 563	4 608	1 689	28	0	0
East Java	178	8 896	36 120	2 284	1 448	264	20	0	0	0
Kalimantan:										
West Kalimantan	0	0	603	133	1	72	41	0	0	0
Central Kalimantan	0	0	2 106	162	4	0	0	0	0	0
South Kalimantan	0	0	5 621	1 863	314	9	0	0	0	0
East Kalimantan	0	2	0	0	218	0	0	0	0	0
West Nusa Tenggara	0	0	123	19 632	1 199	0	0	0	0	0
Sulawesi:										
North Sulawesi	0	0	0	0	0	0	1	0	0	0
Central Sulawesi	0	0	2	0	0	0	0	0	0	0
South-east Sulawesi	0	0	0	9	6	0	0	0	0	0
South Sulawesi	0	386	149	71	664	101	832	1 721	1 451	0
Sumatra:										
Aceh	0	35	694	1 000	143	5	0	122	0	0
North Sumatra	0	1 373	2 843	297	378	508	873	1 217	285	0
West Sumatra	150	1 262	2 695	1 244	0	0	350	23	0	0
Riau	0	162	140	138	16	22	775	526	22	0
Jambi	0	0	0	12	0	0	201	1 504	147	0
South Sumatra	833	359	1 054	1 048	328	901	748	220	0	0
Bengkulu	0	0	0	0	0	0	0	0	0	0
Lampung	146	61	0	329	97	78	82	100	0	0
Indonesia, total	17 431	17 213	56 359	35 283	13 478	17 350	17 972	10 081	2 100	34

[a] No cases were reported from Maluku, East Nusa Tenggara or West Irian during this period.

geographical distribution of the disease. Not only did villages and regencies fail to report to provincial authorities, but many provincial administrations submitted no reports to the national authorities. The number of cases officially recorded at the national level varied from 1000 to 10 000 during the period 1952–1962. Better data are available for the years 1963–1967, because smallpox control staff visited each of the provinces during 1968 to compile provincial data from previous years in order to obtain baseline information. In 1963, 17 431 cases were recorded, of which all but 3658 were from West Java (Table 13.7). The most complete data available pertain to the years 1965–1967, and these show a wider dispersion of smallpox throughout the central and western islands of Indonesia.

Major epidemics were reported in 2 areas during the period 1965–1967 (Fig. 13.4). In 1965, East Java reported 36 120 of the 56 359 cases recorded in Indonesia and this epidemic was followed in 1966 by one in neighbouring West Nusa Tenggara. Central and South Kalimantan experienced epidemics in 1965, which gradually subsided over the next 2 years without a planned vaccination campaign. Other provinces of Indonesia also reported significant numbers of cases, but because of inadequate reporting few conclusions can be drawn about the comparative magnitude of the smallpox problem in these areas. That reporting was seriously deficient was shown in the January 1968 survey in Java. In this survey, estimates of recent smallpox incidence were derived from the prevalence of facial pockmarks. The survey revealed that, at most, 10% of all cases were actually being reported. Thus, it was calculated that more than 100 000 cases had occurred in 1967 in Java alone. Reporting from the other islands, in which the health resources were fewer, was much less complete than in Java.

ORGANIZATION OF THE PROGRAMME, JANUARY–JUNE 1968

Dr Sulianti lost no time in setting the eradication programme in motion. As a first step she changed a meeting on tuberculosis vaccination scheduled for February 1968 into a planning seminar for smallpox eradication. It was to be the first of a series of annual national meetings which reviewed the programme's progress and established specific plans and targets for the succeeding year. Those attending included Dr Sulianti's staff; senior health officials from the provinces, regencies and municipalities; directors of

Estimates of the Completeness of Case Notification

It was common knowledge that many cases of smallpox were not reported to the health authorities but the general belief was that the true figure was not more than perhaps 2–3 times the number of recorded cases. The fact that 10 067 cases were known in 1967 to have occurred that year was of concern to health officials but it was not cause for real alarm. Dr Keja suspected that underreporting was a much more serious problem and performed a number of simple calculations to estimate its magnitude. The 1968 survey teams had found that 39 out of 8636 children under 1 year of age had the characteristic facial pockmarks and thus had contracted smallpox during the preceding year, 1967. Extrapolating from this rate of 4.5 cases per 1000 to the entire population of children under 1 year (2 457 000), Dr Keja arrived at a figure of 11 056 cases. However, since Indonesian data showed that 40% in this age group died of smallpox, he reasoned that the actual number who had had smallpox was 1.67 times larger. Making further corrections to allow for the fact that at least 10% survived without recognizable pockmarks, and calculating that those under 1 year of age accounted for not more than one-fifth of all smallpox cases, he estimated that at least 100 000 cases of smallpox had occurred during 1967 in Java alone, or 10 times more than the number recorded. The numbers in the survey were small and the method of estimation, although unsophisticated in statistical terms, was understandable to non-technical people. The Minister of Health was incredulous and asked other statisticians to examine the data. All of Dr Keja's assumptions served to understate the magnitude of the problem. Case-fatality rates among infants under 1 year were nearer 50% than 40%; the proportion of those surviving without recognizable pockmarks was closer to 35% than 10%; and the proportion of cases in Indonesia among those under 1 year was actually 14% rather than 20%. Finally, Dr Keja had made no effort to correct the estimate to reflect the fact that the children who were examined were all less than 1 year of age and thus, on average, had actually been exposed to smallpox only over a 6-month period. His decision to develop a conservative but understandable estimate had been deliberate. The figure of 100 000 cases was impressive in itself. When Indonesian statisticians independently made their own estimates, they calculated that the number of cases had more likely been in the range of 200 000–500 000. The Minister was persuaded that smallpox was indeed a problem of high priority in Indonesia.

maternal and child health, school health and malaria control programmes; and representatives from the armed forces, the Ministry of Home Affairs and the Central Bureau of Statistics. The seminar represented a laudable effort to involve a wide range of civil and military authorities in the programme although, in fact, few of those present were to make significant contributions until late in its course.

It was decided to launch the programme in June 1968 in Java and Bali, in which 66% of the population lived, and to extend it to the outer islands a year later. Additional vaccinators would be appointed for each subdistrict (40 000–50 000 population), which would more than double the number then in the field. However, they would work only part time, as did the others, because their pay remained low. A supervisor would be appointed for each regency (500 000–1 000 000 inhabitants) and additional supervisory staff would be provided at provincial and national levels. In each of the 90 regencies and the 6 provinces, a "fire-fighting" team of 3 or 4 persons would be formed from existing staff specifically to contain outbreaks.

Because the vast majority of cases were occurring among the unvaccinated, vaccinators were instructed to concentrate on primary vaccination. The maternal and child health centres were directed to vaccinate all infants attending clinics (estimated to represent about 40% of the total number of infants) and the school health services to vaccinate all schoolchildren (corresponding to about 50% of all children of school age). The newly developed bifurcated needles and the multiple puncture technique of vaccination would be employed by all vaccinators

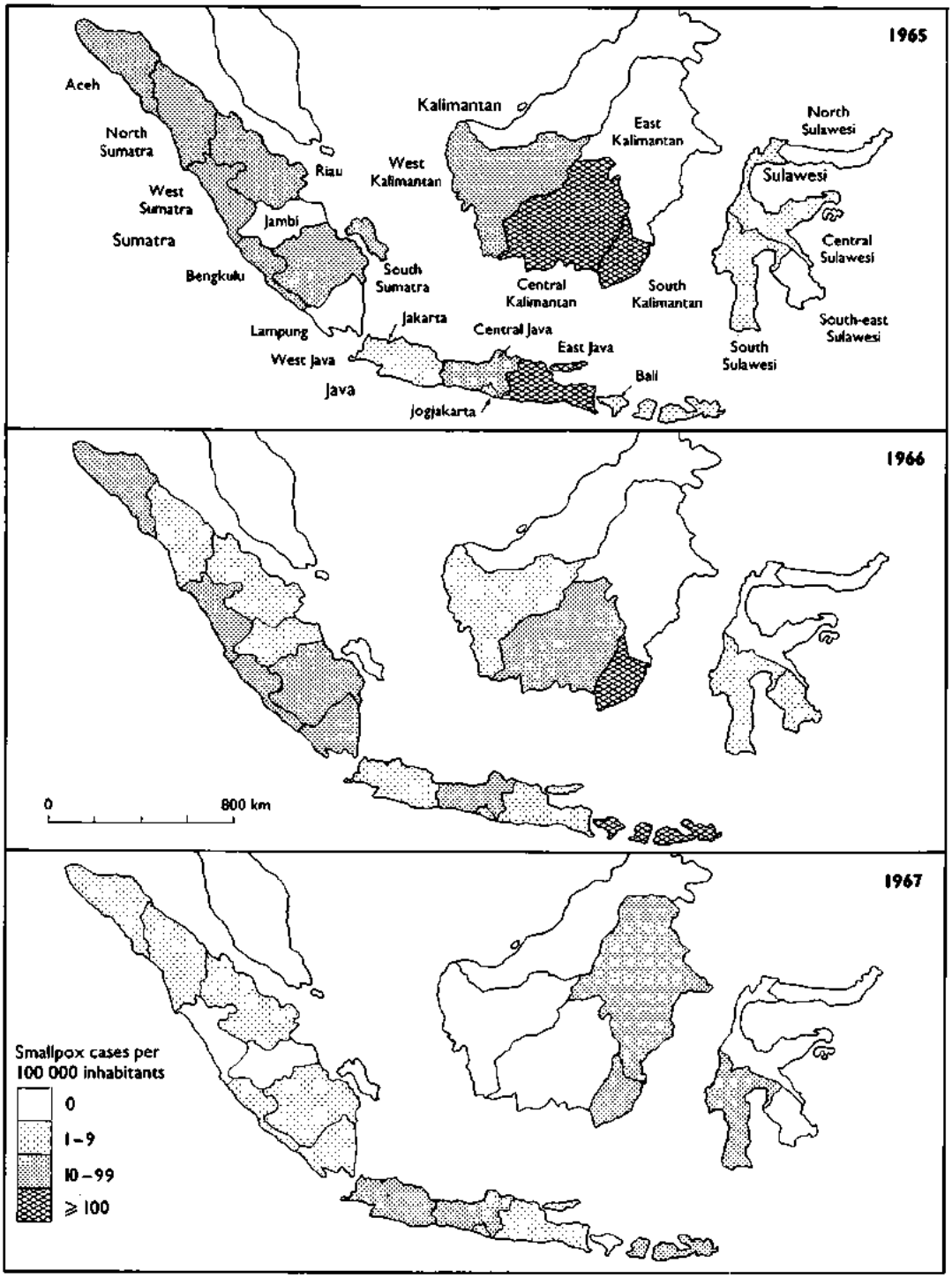


Fig. 13.4. Indonesia: number of reported cases of smallpox per 100 000 inhabitants, 1965–1967.

except the members of national surveillance–containment teams, who would use jet injectors supplied by WHO. It was agreed that only freeze-dried vaccine would be employed, that cold-storage depots would be established at national, provincial and regency levels, and that each batch of vaccine produced by the Biofarma laboratory would be tested by WHO

Table 13.8. WHO support for the Indonesia programme, 1967–1974 (US$)[a]

Year	WHO personnel	Local costs	Supplies and equipment	Total
1967	-	164	121 081	121 245
1968	15 544	19 674	204 562	239 780
1969	40 499	48 000	70 947	159 446
1970	70 269	63 618	18 156	152 043
1971	70 117	66 186	36 548	172 851
1972	56 624	68 157	45 595	170 376
1973	53 785	58 344	52 674	164 803
1974	47 299	53 971	18 549	119 819
Total	354 137	378 114	568 112	1 300 363

[a] Excluding the cost of supplies of vaccine.

Table 13.9. Indonesia: principal items of equipment provided by WHO, 1968–1971

Equipment	1968	1969	1970	1971	Total
Vehicles	15	4	2	3	24
Motor cycles	135	135	160	0	430
Bicycles	1 550	1 550	0	0	3 100
Outboard motors	0	9	10	0	19
Refrigerators	23	16	34	0	73
Jet injectors	25	0	0	0	25

laboratories and released for use only after certification that it met WHO standards of potency, stability and bacterial content.

In support of the programme, WHO eventually provided a total of US$1 300 363 to cover the purchase of supplies and equipment, local costs and staff costs (Tables 13.8 and 13.9); it also provided for the acquisition of 4.1 million doses of vaccine. Indonesia's expenditure amounted to US$3 600 000. The total outlay was equivalent to just over US$0.04 per head of population.

The central staff initially consisted of 4 medical officers (later increased to 8), 7 health inspectors (later 10) and 12 administrative staff. A WHO medical officer was assigned throughout the programme (Dr M. F. Polak, July 1968–January 1969; Dr Reinhard Lindner, January 1969–July 1971; Dr G. G. O. Cuboni, May 1971–1973), and an operations officer, Mr William Emmet, was appointed in August 1970. WHO short-term consultants assisted for a period of approximately 24 man-months.

The programme was conducted by a specially created Smallpox Eradication Unit in the Directorate of Epidemic Control under the direction of a motivated and committed physician, Dr P. A. Koswara. This unit, in turn, reported to Dr Sulianti. At the provincial level, there was a smallpox eradication programme section, also headed by a full-time medical officer. At the regency/municipality level, the responsibility for the programme rested with a medical officer assisted by an experienced senior sanitarian and one or more assistant supervisory sanitarians.

THE EARLY STAGES OF THE PROGRAMME, JUNE 1968–JULY 1969

At the beginning of the programme, preoccupation with the vaccination component was perhaps inevitable. This approach had proved effective in the late 1930s, despite reliance on the use of thermolabile glycerolated vaccine in the main islands and a variably potent but stable room-dried vaccine in more distant areas. National and WHO programme staff believed that with an already high level of immunity, the increased number of vaccinators, using a freeze-dried vaccine of assured potency, should be able to find and vaccinate the comparatively small proportion of susceptible people and so interrupt transmission rapidly. As would prove true in other countries of Asia, this strategy did not work.

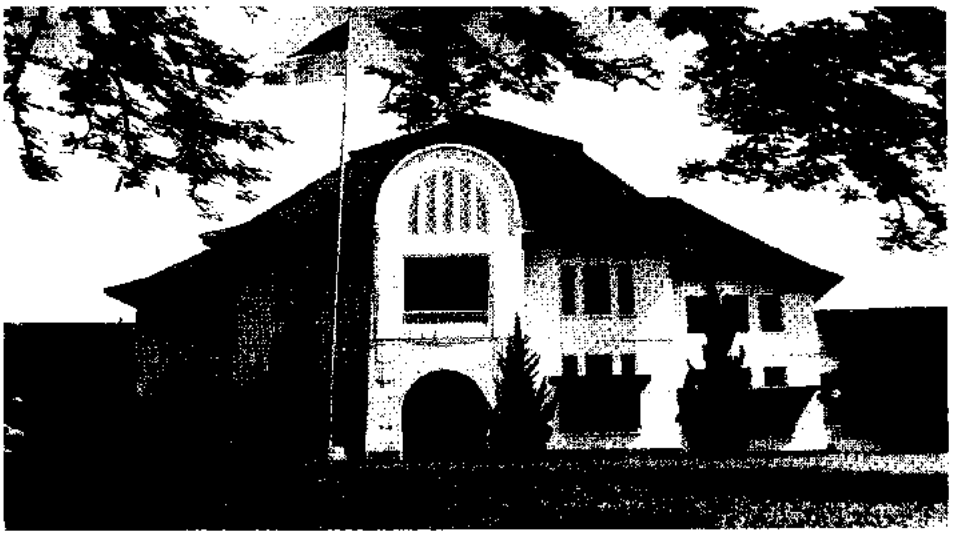
Throughout Indonesia, 3130 vaccinators —approximately 1 for each subdistrict—and 324 regency supervisors conducted the programme. On average, this amounted to 1 vaccinator for every 39 000 persons, the ratio ranging from 1 to 9000 in sparsely inhabited areas to 1 to 50 000 or more in densely populated regions. The pre-war procedure, according to which vaccinators visited each

Plate 13.3. Petrus Aswin Koswara (1931–1974), directed the national programme until April 1972. Standing at centre, he is speaking with Dr Hasan Anoez, Provincial Medical Officer in South Sulawesi, and D.A. Henderson in 1971.

village 4 times a year to give primary vaccinations and one-third of all villages to perform revaccinations, was modified to emphasize primary vaccination. During 8 weeks of each quarter, vaccinators were instructed to visit all villages to give primary vaccination to all preschool children (up to 4 years of age), including newborn infants. During the remaining 5 weeks, they were instructed to visit one-quarter of all villages to vaccinate or revaccinate all children aged 5–14 years. The programme was modified in Bali, in which vaccination was entrusted to malaria surveillance workers. If well executed, this intensified campaign would have ensured, within 1 year, vaccinial immunity in nearly all children from birth to 14 years of age, the age group in which most cases were occurring.

The problems of vaccine supply and quality were gradually resolved over a period of 18 months. Biofatma ceased production of the liquid and room-dried vaccines and began to produce freeze-dried vaccine only. UNICEF provided additional vaccine production equipment and WHO recruited consultant assistance for the laboratory. Better methods of quality control, as well as improved production methods, were instituted. By the end of 1968, the quality of the freeze-dried vaccine began to meet accepted WHO standards and, during 1969, the laboratory began to produce sufficient vaccine to meet Indonesia's needs. In the meantime, vaccine donated to WHO by New Zealand, Thailand, the USSR and the USA augmented the supply. National and provincial cold-storage depots were already available; WHO provided additional refrigerators for use at the regency level. To simplify procurement and distribution, the national health authorities decided to purchase all vaccine from Biofarma with national funds and to distribute it without charge to provincial health departments, which, in turn, were to distribute the vaccine to regencies.

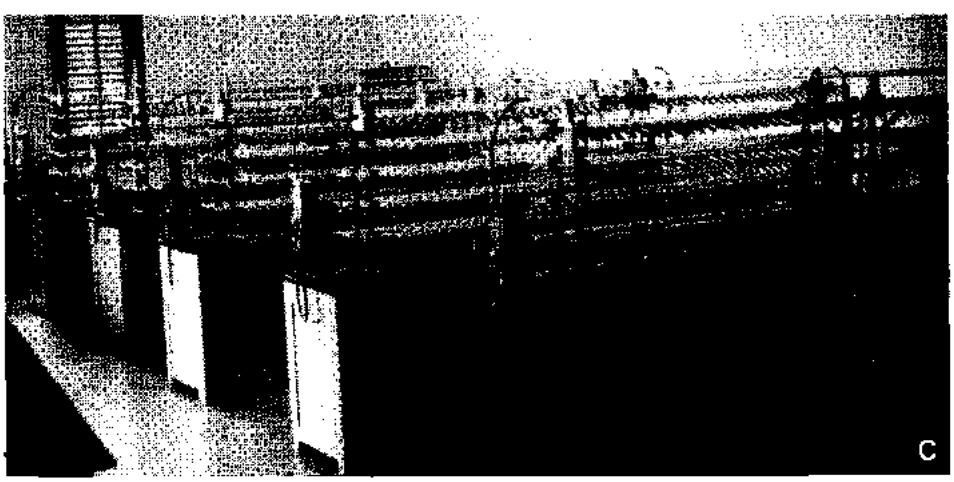
Not surprisingly, a host of problems arose in a programme which was to be so greatly strengthened and executed in such a large population with only 6 months of preliminary planning and organization. One by one, these difficulties were resolved. To cite a few of the more important: deliveries of vehicles, bicycles and other items transported by sea were delayed by months because of customs



BIO FARMA

B

BY COURTESY OF D A HENDERSON



C

BY COURTESY OF D A HENDERSON

Plate 13.4. Biofarma laboratory, Bandung, (**A**) which produced smallpox vaccine for the programme. As late as 1968, room-dried vaccine was still being prepared by the procedure introduced by Otten in 1926. The vaccine pulp was dried in desiccators (**B**), after which it was put in vials which were sealed under vacuum (**C**). The vaccine was remarkably heat-stable but difficult to produce and was often contaminated with bacteria.

clearance formalities; government fiscal procedures were cumbersome and payments for vaccine to Biofarma were held up, resulting in the periodic cessation of production in late 1968 and 1969; payments to staff were similarly interrupted from time to time, with a consequent suspension of work; the recording of cases and transmission of data were seriously deficient; and effective supervision at the beginning of the programme was minimal. All these problems had to be dealt with more or less simultaneously and all persisted to some degree or recurred throughout most of the programme.

For the vaccination campaign, it was decided to establish an annual target for primary vaccinations equivalent to 6% of the population and one for revaccinations equivalent to 30% of the population. It was an unrealistic expectation, given that the vaccinators worked only part time and that the supervision and planning of vaccinator tour schedules were marred by lack of experience. Vaccinators on average performed only 20–80 vaccinations per day, of which between 2 and 20 were primary vaccinations. The programme never met its targets, although it began to approach them in 1970 (Table 13.10). A repeat stratified cluster sample survey in June 1969, similar to that performed in January 1968, showed no significant change in the proportion of susceptible persons (*Wkly epidem. rec.*, 1969c).

The plan had called for "fire-fighting teams" at regency level to contain outbreaks, but few of the regency teams functioned well—and most of them not at all—because of lack of interest and motivation. Vaccination to control outbreaks was neither thorough nor systematic; the sources of cases were not traced, and few of the locales of outbreaks were revisited to ensure that transmission had been stopped.

Indonesia, so densely populated, had seemed to be an ideal place to use jet injectors in outbreak containment. The injectors were provided by WHO and, in August 1968, a consultant was recruited to train special vaccination teams in their use and maintenance. As was true in many other areas, the concept was attractive in theory but disappointing in practice. Except in urban areas, the population was not accustomed to gathering in large numbers at collecting points, and unless they did so the considerable capacity of the injectors could not be realized. Maintenance and repair of the injectors and the logistics of providing a flow of spare parts proved to be formidable obstacles. Within a year, the jet injectors had been abandoned in favour of bifurcated needles. Not only did the latter yield far better results in comparison with the old vaccinostyle (as was revealed in a short trial in Ciloto, West Java) but they also proved to be considerably more economical in the use of vaccine. Beginning in March 1969, the bifurcated needle was accepted as the standard equipment for vaccination in the programme.

Improvement in the supervision and execution of the programme was needed at all levels and, to effect this, 13 "advance teams" (1 each in Jakarta, Jogjakarta and Bali, 2 in East Java and 4 each in West and Central Java) were established in January 1969. These teams provided a critical link in supervision between the national programme directorate and the regencies and were ultimately instrumental in instituting an effective surveillance–containment programme. They were given a month of special training and sent to the field. Each team was provided with a WHO vehicle and was headed by a physician who was able to work full time in the programme, thanks to a salary subsidy paid by WHO. The initial plan called for the teams to spend two-thirds of their time in surveillance and containment activities and one-third in improving the supervision of vaccinators.

Table 13.10. Indonesia: number of primary vaccinations and revaccinations, 1968–1973

Year	Number of vaccinations			Percentage of population covered	
	Primary vaccinations	Revaccinations	Total	Primary vaccination	Revaccination
1968	3 565 995	13 372 121	16 938 116	3.1	11.6
1969	4 088 302	22 764 044	26 852 346	3.5	19.4
1970	5 755 770	27 058 671	32 814 441	4.8	22.5
1971	4 957 651	19 668 733	24 626 384	4.0	16.0
1972	3 849 808	8 843 681	12 693 489	3.1	7.0
1973	3 874 766	6 329 022	10 203 788	3.0	4.9

Table 13.11. Indonesia: number of reported cases of smallpox by province and month, 1969[a]

Province	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
Java:													
West Java	1691	1011	889	1199	836	837	826	620	914	1316	793	1034	11966
Jakarta	66	35	45	60	43	28	11	37	34	21	9	3	392
Jogjakarta	1	1	0	0	0	0	0	0	0	0	0	0	2
Central Java	467	162	141	160	136	137	231	119	66	19	20	31	1689
East Java	16	1	0	0	0	0	0	0	0	2	1	0	20
Kalimantan:													
West Kalimantan	2	3	14	5	2	2	3	1	1	7	1	0	41
Central Kalimantan	0	0	0	0	0	0	0	0	0	0	0	0	0
South Kalimantan	0	0	0	0	0	0	0	0	0	0	0	0	0
East Kalimantan	0	0	0	0	0	0	0	0	0	0	0	0	0
Sulawesi:													
North Sulawesi	0	0	1	0	0	0	0	0	0	0	0	0	1
Central Sulawesi	0	0	0	0	0	0	0	0	0	0	0	0	0
South-east Sulawesi	0	0	0	0	0	0	0	0	0	0	0	0	0
South Sulawesi	2	2	0	0	39	62	92	259	110	107	76	83	832
Sumatra:													
Aceh	0	0	0	0	0	0	0	0	0	0	0	0	0
North Sumatra	61	15	34	18	2	23	189	101	107	160	55	108	873
West Sumatra	15	4	0	0	85	68	55	46	30	6	21	20	350
Riau	0	0	0	0	0	73	82	570	16	20	2	12	775
Jambi	14	0	4	0	0	4	11	14	0	42	93	19	201
South Sumatra	64	25	8	86	24	5	3	153	163	102	75	40	748
Bengkulu	0	0	0	0	0	0	0	0	0	0	0	0	0
Lampung	22	12	23	2	2	0	0	0	0	21	0	0	82
Total	2421	1271	1159	1530	1169	1239	1503	1920	1441	1823	1146	1350	17972

[a] No cases were reported in Maluku, Bali, Nusa Tenggara or West Irian during this period.

Despite the chaotic beginning and the numerous problems, remarkable progress was recorded in some provinces (Table 13.11). East Java had experienced major epidemics in 1964 and 1965 and, in consequence, had conducted mass campaigns. However, the vaccination survey of December 1967–January 1968 (see Table 13.5) showed that vaccinial immunity was no better than in West Java and far lower than in Central Java despite the mass campaigns. In July 1968 a dynamic Provincial Director of Communicable Disease Control, Dr Bahrawi Wongsokusomo, and his assistant, Dr Witjaksono Hardjotanojo, took charge of the programme in East Java and vowed that they would interrupt transmission before January 1969. Vaccination activities were intensified, but—more important—any outbreaks found were energetically contained. During the last 6 months of 1968, only 133 cases were detected in the entire province. Between January and June 1969, only 3 outbreaks occurred, each of which could be traced to importations from Central Java; all were well contained after discovery. It was a remarkable achievement, accomplished almost wholly with provincial resources.

In Jakarta, under the leadership of Dr Guno Wiseso, special teams equipped with jet injectors demonstrated the efficacy of the outbreak-containment strategy. During a 3-month period, they investigated and contained 73 outbreaks, in which 217 cases had been reported (*Wkly epidem. rec.*, 1970a). The teams searched for additional cases, endeavoured to find the origins of the outbreaks and vaccinated the inhabitants of the affected administrative units (about 200 persons in each unit), as well as the people living in the 4 surrounding units. During these activities they discovered an additional 215 cases and vaccinated some 73 000 persons. A subsequent assessment revealed that smallpox transmission had ceased within 2 weeks of containment in two-thirds of the outbreaks (Table 13.12). Although these results would be considered poor by later standards, it was clear that outbreaks could, in fact, be quickly stopped.

No smallpox cases were reported in Bali or in the islands to the east after the programme began, and in February 1969 Jogjakarta recorded its last cases. By June 1969, smallpox in Central Java was being reported from only 4 of 35 regencies but West Java continued to report nearly 1000 cases per month. Meanwhile, the complement of vaccinators and supervisors in Java steadily increased and by June had more or less reached the numbers planned (Table 13.13). In Kalimantan, Sulawesi and Sumatra, the programmes did

Table 13.12. Jakarta: number of weeks after containment in which new cases were detected, 1968

	0	1	2	3	4	5	6	⩾7
Outbreaks contained (62)	39	5	5	4	4	0	1	4
Outbreaks still continuing (11)	2	3	1	4	0	1	0	0

Table 13.13. Java: population and number of vaccination staff and supervisors, June 1969

Province	Population (thousands)	Number of regencies/ municipalities	Staff category			Ratio of vaccinators to population
			Part-time medical officers	Supervisors	Vaccinators	
West Java	20 997	24	30	24	392	1:54 000
Central Java	22 268	35	35	33	498	1:45 000
East Java	26 400	37	37	60	555	1:48 000
Jakarta	3 910	5	5	10	78	1:50 000
Jogjakarta	2 711	5	5	5	74	1:37 000
Total	76 286	106	112	132	1 597	–

not officially begin until July 1969, and thus all reports were considered to be suspect.

The number of cases reported in Indonesia between January and June 1969 amounted to 8789, a total not significantly different from the 8847 cases recorded during the same period in 1968. Although the staff believed that there was more complete reporting of cases, it was impossible to measure the extent of improvement. What was certain, however, was that reporting was still incomplete. The reporting of cases to the regency medical officer was the responsibility of village chiefs, but many chiefs completely neglected this task, even though they were aware that cases were occurring. Moreover, some regencies failed to report to the provinces, or, if they did, the reports were greatly delayed. In June, reports from almost one-quarter of all provinces in Java and Bali were overdue by a month or more. Reporting from other provinces was even more delayed and incomplete.

When the programme began, plans had been made for its assessment by a WHO–Indonesia team one year later. In June 1969, this was undertaken and recommendations were developed. The team was sharply polarized on the issue of mass vaccination. One group maintained that, with vaccinial immunity so high, the mass vaccination campaign could be said to have been completed already and that all efforts should be directed to surveillance and containment. A second group argued for a special campaign to move rapidly and systematically throughout the country to vaccinate the now very small proportion of people who had no vaccination scars.

A compromise was reached and the teams recommended that: (1) special programmes should be mounted to deal with the backlog of unvaccinated children under 15 years of age in Jakarta and West and Central Java (the number was estimated to be 3.3 million, or 16.6% of a population of 19.9 million children); and (2) surveillance should be strengthened through improved reporting by village chiefs and other health staff, and more active outbreak containment by the special "fire-fighting" and advance teams. It was recognized that the backlog vaccination campaigns would tax, and perhaps overstrain, available government resources, but the campaign was accepted as a component of the strategy.

THE STRATEGY CHANGES, JULY 1969

The resources available did not permit the implementation of backlog vaccination campaigns throughout the whole of Java, and so priorities were defined. In East Java and the islands to the east, in which transmission had been interrupted, efforts were to be directed solely to the early detection and containment of imported cases. In Central Java, lying immediately to the west, smallpox incidence was declining and prospects for the early interruption of transmission appeared good. Thus, the decision was made for vaccination teams (called "backlog-fighting teams") to begin work in the eastern regencies of Central Java and to move westward in the expectation that smallpox would progressively disappear in an east-to-west direction. Given the prob-

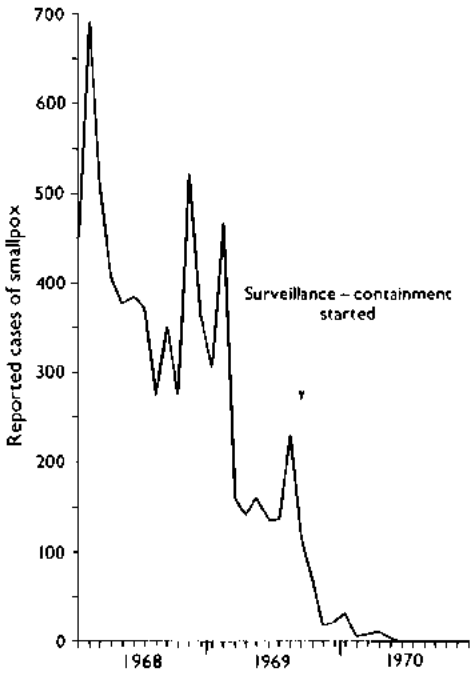


Fig. 13.5. Central Java: number of reported cases of smallpox, by month, 1968–1970.

ability that the situation in West Java would soon follow the same course, backlog-fighting teams were scheduled to commence operations in the province's 7 easternmost regencies.

As the backlog-fighting teams began vaccination in Central Java, the 4 provincial surveillance teams started work in the northwest, where smallpox incidence was the highest. Directed by a capable epidemiologist, Dr P. R. Arbani, these teams concentrated entirely on case detection and outbreak containment. Gradually they extended the scope of their operations to include the whole province. The number of cases in Central Java declined dramatically (Fig. 13.5). In December only 31 cases were detected, and by May 1970 the last case had occurred. The advance teams had performed only 54 000 containment vaccinations, a small fraction of the 5 million vaccinations which were being given annually in the province.

West Java presented a more formidable problem. Provincial supervision had been inadequate for many years and this was reflected in the low levels of vaccinial immunity throughout the province. During the first half of 1969, an average of almost 250 cases had been reported weekly—in a province whose notification system was the poorest in Java. In July, 4 special teams, each consisting of 5 vaccinators and a team leader, were recruited for each of the 7 regencies bordering on Central Java (Koswara in WHO/SE/71.30). As in Central Java, the teams proceeded house by house and village by village, performing primary vaccinations and containing any outbreaks that were found.

By October 1969, it became apparent that smallpox transmission was continuing in West Java, even in regencies in which backlog fighting had been completed. Although the teams were instructed to intensify surveillance–containment activities, few did so. In one regency, Tjirebon, in which no such activities had been conducted (*Wkly epidem. rec.*, 1970a), a WHO adviser was assigned to undertake surveillance–containment activities only. National staff supervised combined surveillance–containment and vaccination programmes in 3 other regencies, including Bandung, in which smallpox incidence remained high. Two months later, in December, a main focus of smallpox in the province was found to be yet another regency, Bogor, in which so far no work was in progress. Resources were all but exhausted and only a single team could be assigned there to conduct a surveillance–containment programme.

Three different types of programme had therefore developed in an unplanned operational experiment: (1) in Tjirebon, backlog vaccination was followed by an intensive

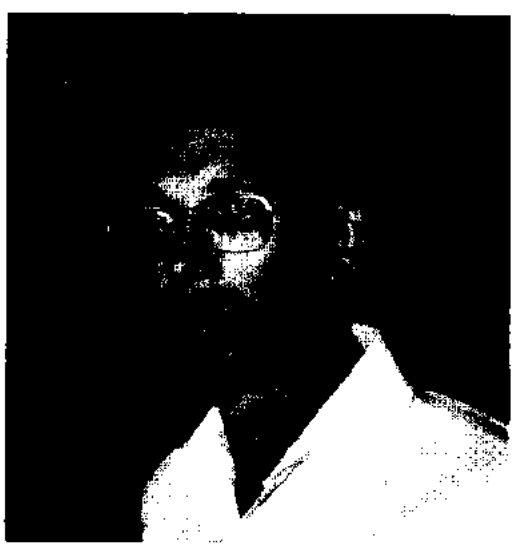


Plate 13.5. Reinhard R. Lindner (b. 1926) was the WHO smallpox adviser to the Indonesian programme from 1969 to 1971.

surveillance–containment programme; (2) in Bandung, a combined backlog vaccination and containment programme was directed by national supervisors; (3) in Bogor, a surveillance–containment programme only was conducted. The results of this experiment were to decide the subsequent strategy of the programme in Indonesia.

Tjirebon Regency

The backlog vaccination operation had begun in July 1969 and ended 18 weeks later. During 2025 man-days, the teams visited 188 287 households in 267 villages. In all, 208 smallpox cases were discovered in 24 villages. On completion of the work, a sample survey showed that the proportion of unprotected children below 1 year of age had decreased dramatically, from 83% to 26%; of those aged 1–4 years, from 36% to 11%; and of those aged 5–14 years, from 3% to 2%. The illusion of a highly successful programme was shattered when just 2 days after the programme had been completed, 12 mobile teams from other provinces undertook a 2-day training exercise in Tjirebon. They discovered that in 7 infected villages transmission was still continuing. By tracing the sources of infection, an additional 118 cases and 3 undetected outbreaks were discovered.

Greater efforts were obviously needed, and a WHO consultant, Mr Michael O'Regan, was assigned in mid-November. On arrival, he found a frustrated but hard-working staff with a disorganized record system and no day-to-day operational programme. In the yaws and leprosy programmes in which Mr O'Regan had worked, methods had been developed for the systematic search for cases throughout extensive areas. Applying similar principles in Tjirebon, he obtained reliable maps and lists of villages from the army and, with regency staff, planned a programme consisting of a systematic village-by-village search for cases and house-to-house searches when outbreaks were found. The basic work was performed by 7 search teams each composed of 2 men on bicycles, their work being supervised by 2 search teams with vehicles. In every village, the programme was explained to the village leader and assurances were given that, should he report a case, a team would come to the village within 24 hours. Outbreaks, when discovered, were contained and the locality concerned was revisited weekly until 4 weeks after the last case had occurred. Identification of the source of each outbreak permitted the discovery of other, unreported outbreaks. Each night the staff met, reported their findings and planned the following day's work. The initial search revealed that, as at 1 December 1970, there were 31 villages with active cases, but within 2 months transmission had been interrupted (Fig. 13.6).

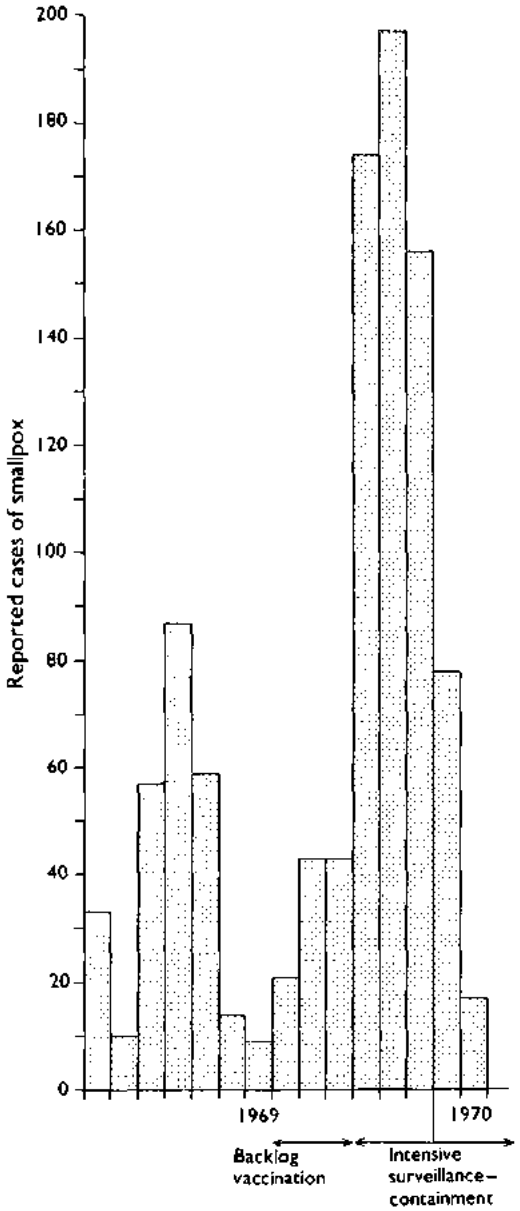


Fig. 13.6. Tjirebon Regency: number of reported cases of smallpox, by 4-week intervals, 1969–1970. The last interval in 1970 includes 6 importations and 11 delayed reports of inactive cases.

Cases continued to occur as a result of importations from other regencies but these were quickly contained. The Tjirebon programme was the first in the Intensified Programme in which teams undertook a systematic area-wide search for cases without simultaneously performing vaccinations. The technique was later to be widely applied throughout Indonesia and was to prove vital in interrupting transmission in the Indian subcontinent.

Bandung Regency

In Bandung, the combined surveillance–containment and backlog-fighting operation under the supervision of national staff had begun early in November 1968 and ended 26 weeks later. The teams visited 401 490 households in 242 villages and performed 163 194 primary vaccinations; 74 outbreaks with 565 cases were detected and contained. Altogether 4020 man-days were required. The resources needed to interrupt transmission were even greater than those expended in the Tjirebon programme.

Bogor Regency

A single surveillance team with a vehicle had been assigned to Bogor in December 1969, after a national team investigating a reported outbreak discovered that not 1 but 18 out of 24 subdistricts were infected. Because no additional resources could be spared, the team continued to work alone. During 42 weeks, active search and containment detected 2101 cases in 101 villages, but transmission was completely interrupted; only 15 175 containment vaccinations were performed. Time was required to interrupt transmission in this densely populated area, but it was achieved at a cost of only 1802 man-days.

Plate 13.6. Vaccinators in Indonesia moved from house to house, concentrating their efforts on young children and infants who had not been vaccinated previously. For this work, the bifurcated needle was especially valuable.

Factors Affecting Transmission

In October 1970, after transmission had been interrupted in the 3 regencies, surveys were conducted to determine comparative levels of vaccinial immunity (Table 13.14).

Smallpox transmission had been rapidly interrupted in Tjirebon once surveillance–containment measures had been effectively applied, but vaccinial immunity was already

Table 13.14. Tjirebon, Bandung and Bogor Regencies: percentage of children unprotected by vaccination, by age group, October 1970[a]

Age group (years)	Percentage of children unprotected			
	Tjirebon	Bandung	Bogor	
			Less endemic area	Highly endemic area
<1	28	44	86	66
1–4	11	12	46	32
5–14	6	7	23	18
0–15	12	14	39	30
Number of children examined	8 342	8 480	7 685	9 566

[a]Based on Koswara (in WHO/SE/71.30).

high there. Success had also been achieved in Bandung with improved supervision but at a considerable cost in resources. Bogor presented a contrast. There, transmission had also been successfully interrupted with surveillance–containment only, although 2–3 times as many unprotected children remained. The proportion that was unprotected was almost as high in the infected areas—in which containment vaccination had been extensive—as it was in the less endemic areas.

Everyone involved in the programme was surprised by the tenacity of smallpox in these and other regencies of Java despite comparatively high levels of vaccinial immunity and intensive surveillance–containment measures. It was a contrast to the situation in Brazil and western Africa, in which surveillance and containment had quickly stopped transmission, even in less well vaccinated populations (see Chapters 12 and 17). Indonesia, demographically and socially, was different in several respects (*Wkly epidem. rec.*, 1970a). Population density in Java was one of the highest in the world and, traditionally, families carried children who were sick from house to house to visit relatives. The tradition of isolating cases, so often observed in other countries, was uncommon. Thus, many more susceptible persons, on average, were exposed to smallpox cases than in most other areas. Because of high levels of vaccinial immunity and the greater frequency of exposure of susceptible persons, the age distribution of cases was different in Java from the corresponding distributions in Brazil and Pakistan, for example (Table 13.15).

Table 13.15. Comparative percentage distribution of smallpox cases, by age group, 1969[a]

Age group (years)	Jakarta	West Java	Brazil	Pakistan
0–4	58	56	36	29
5–14	37	33	37	39
⩾15	5	11	28	31

[a]Based on Hartohusodo (in WHO/SE/71.30).

In Java, more than half of all cases were found in children under 5 years of age; few cases occurred in adults. In Africa, South America and Asia, cases were more evenly distributed among all age groups.

Another factor of importance in smallpox transmission in Indonesia was climatic: smallpox was readily transmitted throughout the year (Fig. 13.7). Indonesia, located between 5°N and 5°S of the equator, did not have the wide seasonal fluctuations in transmission which were characteristic of countries such as Brazil, India and Pakistan (*Wkly epidem. rec.*, 1969a) (see Chapter 4). In these countries, in which transmission rates declined sharply during the summer and early autumn months, many chains of transmission terminated spontaneously and the containment of outbreaks during these periods was comparatively simple. In Indonesia no such circumstances obtained.

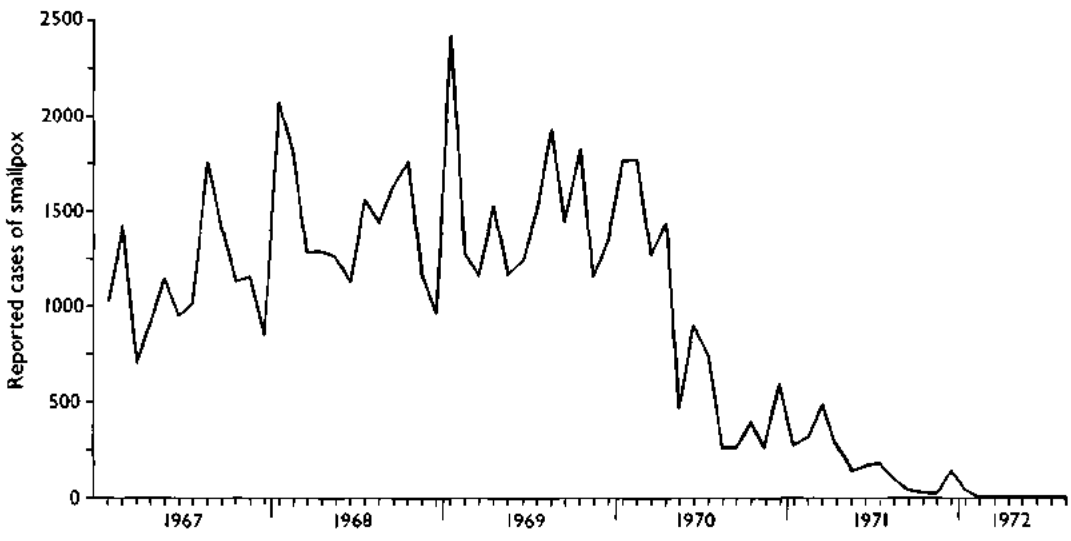


Fig. 13.7. Indonesia: number of reported cases of smallpox, by month, 1967–1972.

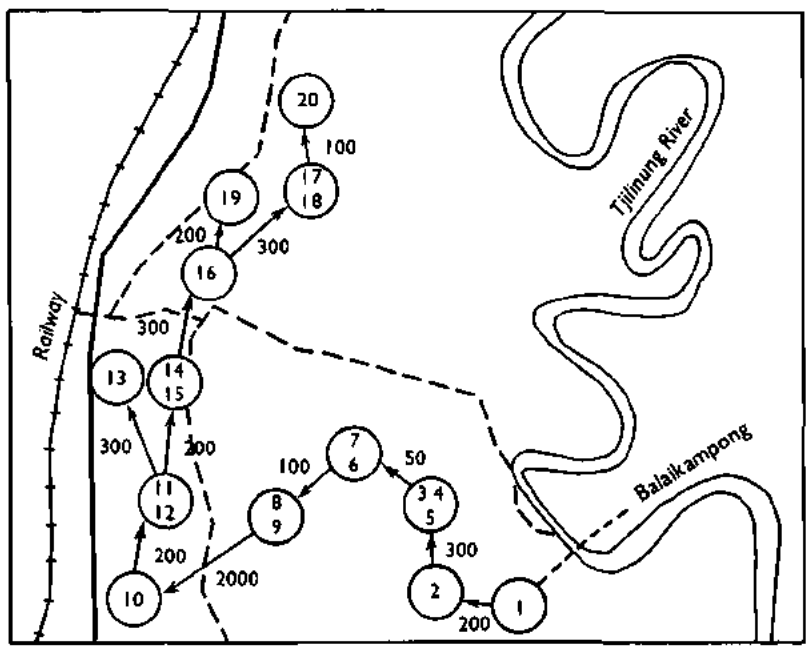
Smallpox Transmission in a Well-Vaccinated Area

An outbreak in Passar Minggu (population, 14 376), a densely populated section of Jakarta City, vividly illustrated the ability of smallpox to continue to be transmitted even in well-vaccinated areas. In August 1970, the investigation of a death due to smallpox led to the discovery of a chain of infection involving 20 cases extending over a period of 21 weeks (see the figure below). A scar survey in the area revealed that only 2% of children between 5 and 14 years of age were unvaccinated (see table). Overall, the proportion of susceptible persons in the area was only about 6%, almost none of whom were adults.

Passar Minggu: Vaccination Status of Children and Cases of Smallpox
(Emmet in WHO/SE/71.30)

Age group (years)	*Percentage unvaccinated*	*Number of cases*
<1	61%	2
1–4	20%	11
5–14	2%	5
⩾15	–	2

The cases spread from one house to the next, usually over a distance of no more than 300 metres (see illustration). Nine of the cases resulted from intrafamilial transmission; the remainder occurred through the visits of susceptible children to infected households.



1 Denotes the presence of a case in a household and the case number assigned to it.

200 → Indicates the distance, in metres, between households.

Similar occurrences of slowly spreading endemic smallpox in well-vaccinated populations were observed throughout the rural areas of West Java and, to some extent, of Central Java. In the other endemic areas of Indonesia, none of those which experienced smallpox after 1968 was so densely populated and smallpox there was far more easily contained.

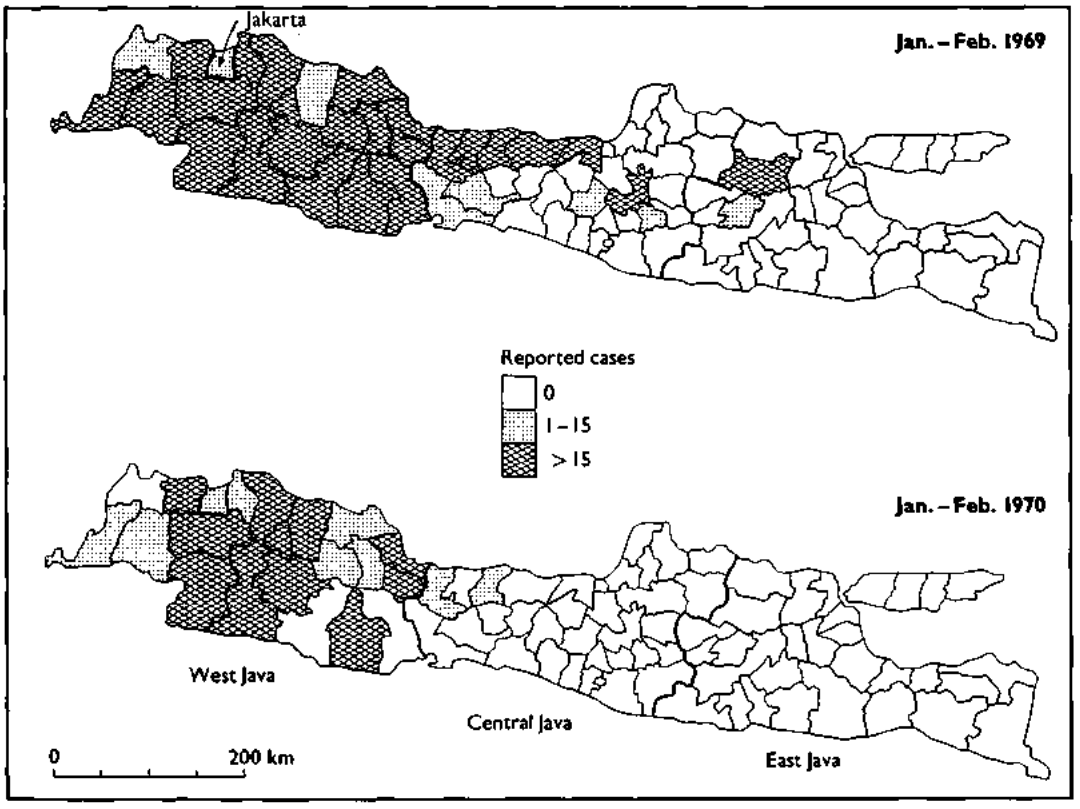


Fig. 13.8. Java: number of reported cases of smallpox, by regency, January – February 1969 and January – February 1970.

THE SURVEILLANCE–CONTAINMENT STRATEGY BECOMES FULLY ESTABLISHED

Despite the problems of the backlog vaccination campaign and the diversion of resources from surveillance–containment activities, progress was made in the "east-to-west" strategy in Java (Fig. 13.8). By February 1970, endemic smallpox remained solely in West Java. In Central Java, during 1970, only 28 cases were detected, all of which represented outbreaks due to importations. Meanwhile, programme activities were extended to the outer islands.

Reporting, which had been so incomplete and greatly delayed, improved markedly in 1970 following the assignment of a full-time medical officer, Dr A. Karyadi, to assume responsibility for surveillance and data collection. Simplified standardized reporting forms were adopted for the weekly reports and a goal was set for the receipt of reports with a delay of no more than 2 weeks from provinces in Java and of no more than 3 weeks from the outer islands (Karyadi in WHO/SE/71.30). Defaulting provinces were repeatedly contacted by letter, telegram, messenger and personal visits to promote compliance. Cooperation was sought from civil authorities as well. In the absence of an adequate postal service, many methods were utilized for the transmission of provincial reports, including couriers such as bus drivers, businessmen, special messengers and military personnel. Provincial authorities, with assistance from the smallpox eradication staff, sought to obtain promptly the weekly reports from regency medical officers and health units. To simplify reporting, the data requested were limited to the names of infected villages and subdistricts, the numbers of cases and deaths, the ages of cases, and the source of infection of each outbreak. Beginning in May 1970, a national weekly surveillance report was prepared which documented smallpox incidence and progress in the campaign. This was distributed to health authorities throughout Indonesia. In September 1970, Dr Karyadi was able to report that 95% of weekly reports were being received from provinces in Sumatra and Sulawesi within 3 weeks. Just one year pre-

Table 13.16. Indonesia: number of reported cases of smallpox, by province and month, 1970[a]

Province	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
Java:													
West Java	1 153	1 123	679	701	242	210	169	88	20	63	36	6	4 490
Jakarta	2	2	1	14	1	0	23	4	39	0	1	43	130
Central Java	5	8	11	4	0	0	0	0	0	0	0	0	28
East Java	0	0	0	0	0	0	0	0	0	0	0	0	0
Sulawesi:													
North Sulawesi	0	0	0	0	0	0	0	0	0	0	0	0	0
Central Sulawesi	0	0	0	0	0	0	0	0	0	0	0	0	0
South-east Sulawesi	0	0	0	0	0	0	0	0	0	0	0	0	0
South Sulawesi	232	340	102	65	42	161	175	34	103	130	101	236	1 721
Sumatra:													
Aceh	0	0	56	55	1	0	0	0	0	6	0	4	122
North Sumatra	34	26	61	220	108	171	214	132	54	60	99	38	1 217
West Sumatra	3	0	6	12	0	0	0	0	0	0	0	2	23
Riau	40	0	0	0	34	324	35	0	0	76	0	17	526
Jambi	283	248	318	229	11	7	102	0	24	19	17	246	1 504
South Sumatra	15	20	10	78	27	15	13	6	0	36	0	0	220
Bengkulu	0	0	0	0	0	0	0	0	0	0	0	0	0
Lampung	0	1	0	58	2	10	12	5	12	0	0	0	100
Total	1 767	1 768	1 244	1 436	468	898	743	269	252	390	254	592	10 081

[a] No cases were reported in Maluku, Kalimantan, Bali, Nusa Tenggara, West Irian or Jogjakarta during this period.

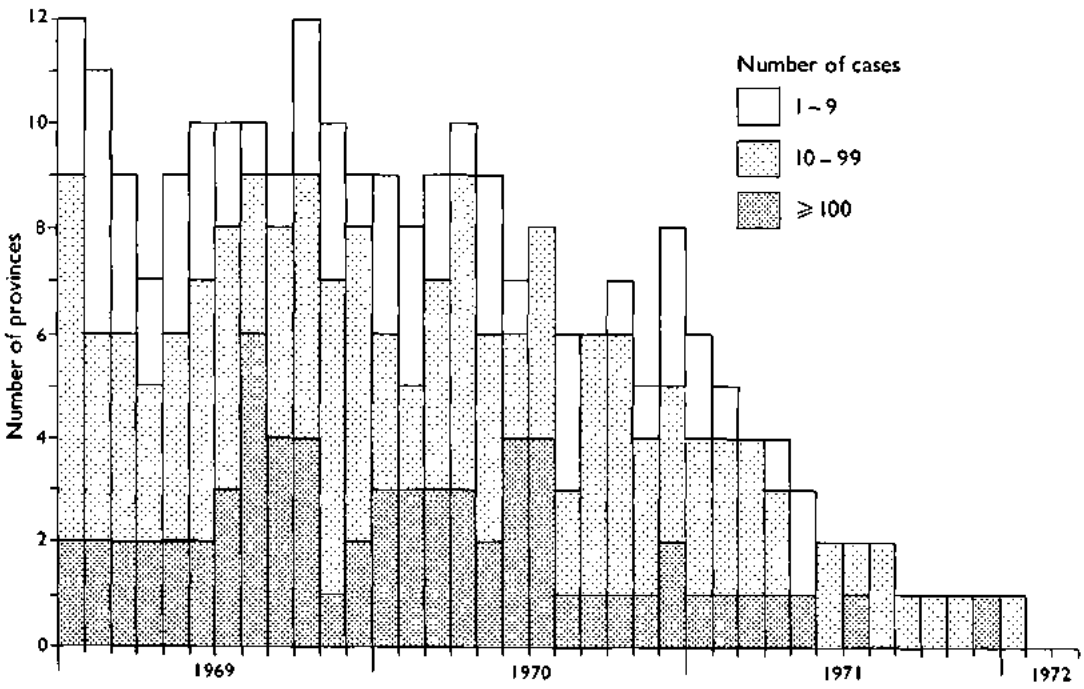


Fig. 13.9. Indonesia: number of provinces reporting cases of smallpox, by month, 1969 – 1972.

viously, only about half as many reports were being received, and then with delays of up to 21 weeks. An increasing number of cases began to be reported from Sumatra, reflecting better notification (Table 13.16). Despite improved reporting, the number of provinces reporting cases began to fall drastically as from the beginning of December 1970 (Fig. 13.9).

In West Java, 8 mobile surveillance–containment teams worked with regency teams in carrying out active search operations and outbreak containment. As the year progressed, area vaccinators devoted less time to routine vaccination and more to systematic searches to detect cases and to contain outbreaks, as was done in Tjirebon. Initially,

The Development and Use of the WHO Smallpox Recognition Card

Events which led to the development of the WHO smallpox recognition card and the use of schools in the search for cases in Indonesia occurred in Bandung. Among the many vaccinators engaged in search activities, there was one who recorded exceptional success in detecting outbreaks. Supervisors noted that, paradoxically, this vaccinator was considered to be one of the laziest workers—the last to leave for the field and the first to return home. When asked how he was so successful, he admitted that instead of visiting all the houses in a village, as instructed, he was visiting only the schools. There he showed children and teachers pictures of smallpox cases which appeared in a WHO teaching folder on smallpox diagnosis that had been prepared for Africa. Numerous case notifications were obtained with the minimum effort.

The teaching folder contained many different pictures of smallpox in African children. The photographs were small and the smallpox rash on a black skin appeared to differ somewhat from the rash on the skin of Indonesians, which was much lighter in colour. Nevertheless, most children had recognized the disease. Programme staff suggested the preparation of a single large picture of an Asian child with smallpox for use as a recognition card. Thus, the WHO smallpox recognition card was first prepared, encased in plastic for durability, and widely distributed around the world.

vaccinators were requested to search house by house, but because of the small numbers of vaccinators available, they were subsequently asked to contact specific persons and the staff of various facilities who would be the most knowledgeable regarding the existence of smallpox cases: (1) health units such as clinics, hospitals and aid posts; (2) civil officials, notably village chiefs, who in Indonesia had considerable authority in their designated areas; and (3) schoolchildren and teachers. Maps were prepared for each area, showing the principal sites and persons to be visited. A tour schedule was established to ensure that each was visited at least once a month. It was during these operations in West Java that the concept arose of printing smallpox recognition cards, depicting in colour a case of smallpox, which could be shown to those being contacted. This idea, which was proposed by Indonesian field staff to WHO regional office and Headquarters staff, was adopted and eventually tens of thousands of such cards were printed and distributed widely in Indonesia and other endemic countries throughout the world (see Chapter 10).

Containment activities were ever more rigorously defined and performed. In each outbreak, the "fire-fighting" or advance teams ensured that patients were isolated in their houses; the names of all villagers were recorded and everybody was vaccinated; the source of infection was identified and investigated; and the teams remained in the village at least overnight to ensure more complete vaccination of those working in the fields or absent during the day at the market or in school.

STRENGTHENING OF PROGRAMMES IN THE OUTER ISLANDS, 1970

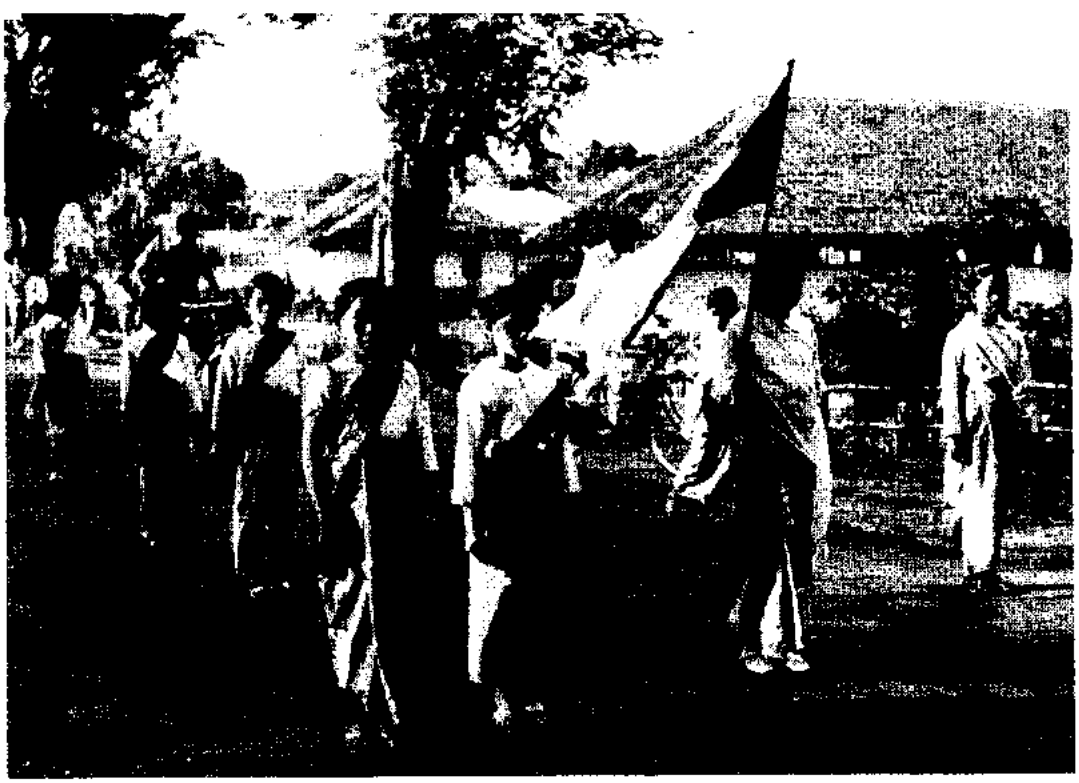
Until 1970, resources and energies were principally directed to the containment of smallpox in the heavily populated island of Java. With the number of cases declining rapidly in Java during 1970 (from 1160 in January to 210 in June and to 49 in December) additional resources could be diverted to the two outer islands still harbouring smallpox—Sumatra and Sulawesi.

Sumatra had the higher priority because of the extensive inter-island boat traffic with Java. The programme in Sumatra had begun in July 1969 with an intensified vaccination campaign conducted by 567 vaccinators and 73 supervisors. As in Java, this had little effect on smallpox incidence. During 1970, more resources were made available to the programme (*Wkly epidem. rec.*, 1970d), notably transport and assistance from national campaign staff, and the strategy shifted from intensive vaccination to surveillance–containment. Smallpox spread less rapidly in the

more sparsely populated Sumatra and successful containment was easier, but this advantage was counterbalanced by a less-developed health structure and poorer supervision. In Sumatra, priority was given to the southern provinces, those nearest Java, to minimize the risk of importations. In October 1970, South Sumatra recorded its last cases, but the northern provinces (North Sumatra, Jambi and Riau) did not become smallpox-free until August 1971.

Sulawesi also began its programme in July 1969, with 355 area vaccinators and 38 supervisors. Endemic smallpox, however, was found only in South Sulawesi (population, 5 million). Progress was slow: the rugged mountainous terrain made travel difficult; communication with villagers was a problem because 15 different dialects were spoken there; and the civil and health infrastructure, after prolonged and devastating civil disturbances, was less developed than in Sumatra or Java. The interruption of transmission in Sulawesi was to require the best skills of experienced national and WHO staff and the most effective application of now well-defined techniques for case search and outbreak containment.

Only 59 vaccination staff worked in South Sulawesi—less than half the number planned. Throughout 1970 comparatively little progress was made. However, early in 1971, with smallpox transmission all but interrupted in Java and with incidence rapidly diminishing throughout Sumatra, senior national staff and WHO advisers transferred to Sulawesi, and additional automobiles, motor cycles and bicycles were assigned to the programme. The WHO smallpox recognition card began to be used in contacts with schools and civil authorities. In March 1971, a planned programme of meetings with village chiefs and other civil administrators was instituted in order to acquaint them fully with the programme and to solicit their help in the prompt reporting of suspected cases. Many conscientiously fulfilled this responsibility through special search programmes which they independently organized. Isolation of patients in their houses, containment vaccination, both by day and by night, search for the sources of outbreaks and identification of



P. LINDNER

Plate 13.7. Schoolchildren parade in support of the national smallpox eradication programme in South Sulawesi, Indonesia.

Table 13.17. Indonesia: number of reported cases of smallpox, by province and month, 1971[a]

Province	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
Java:													
West Java	9	24	17	12	0	0	0	0	0	0	0	129	186
Jakarta	4	0	0	0	0	0	0	0	0	0	0	0	9
Central Java	0	0	0	0	0	0	0	0	0	0	0	0	0
East Java	0	0	0	0	0	0	0	0	0	0	0	0	0
Sulawesi:													
North Sulawesi	0	0	0	0	0	0	0	0	0	0	0	0	0
Central Sulawesi	0	0	0	0	0	0	0	0	0	0	0	0	0
South-east Sulawesi	0	0	0	0	0	0	0	0	0	0	0	0	0
South Sulawesi	149	155	403	220	130	98	142	73	37	25	19	0	1 451
Sumatra:													
Aceh	0	0	0	0	0	0	0	0	0	0	0	0	0
North Sumatra	40	90	20	30	1	56	34	14	0	0	0	0	285
West Sumatra	0	0	0	0	0	0	0	0	0	0	0	0	0
Riau	12	10	0	0	0	0	0	0	0	0	0	0	22
Jambi	62	35	44	5	1	0	0	0	0	0	0	0	147
South Sumatra	0	0	0	0	0	0	0	0	0	0	0	0	0
Bengkulu	0	0	0	0	0	0	0	0	0	0	0	0	0
Lampung	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	276	314	484	267	132	154	176	87	37	25	19	129	2 100

[a] No cases were reported in Kalimantan, Bali, Nusa Tenggara, West Irian or Jogjakarta during this period.

exposed individuals who had left infected villages were more rigorously executed. With improved surveillance and containment measures and heroic efforts by national and WHO staff, smallpox transmission came to an end in South Sulawesi in November 1971 (Table 13.17).

Immediately after the apparent detection of the last case, the 1208 vaccinators in Sulawesi, Sumatra and Kalimantan searched village by village during a 4-month period, reaching 18 205 (73.5%) of the 24 781 villages in the process. Although 920 suspected cases were examined and 76 specimens were taken, none revealed the presence of smallpox (WHO/SE/74.63, Cuboni et al.).

In the island of Kalimantan (population, 5 million) and in the other provinces of Sulawesi, provincial and local health staff, without significant additional support from national or WHO staff, had unexpectedly succeeded in interrupting transmission as early as November 1969. How this was achieved is not fully documented. Kalimantan had experienced a major epidemic of smallpox, with large numbers of reported cases, during 1965–1967. The epidemic may have begun before 1965, although no earlier data are available. Because reporting was so incomplete, it is probable that the actual number of cases may have been 100 times or so greater than the number recorded.

Programme staff at the time speculated that natural immunity induced by the epidemic, combined with extensive vaccination, had so reduced the number of susceptible persons that transmission was interrupted even though the surveillance–containment programme was much less effective than in other areas. However, a high level of immunity was not the primary explanation for the interruption of transmission in Kalimantan and in Central, South-east and North Sulawesi, as was shown in a February 1974 survey. At that time, Indonesian staff conducted random cluster sample surveys among children throughout these provinces (Table 13.18) (WHO/SE/74.66, Cuboni et al.). In most provinces, more than one-third of all children remained susceptible. Immunity levels were substantially below those in most of Java, in which health services were far more extensive.

Important to the interruption of transmission was the fact that the populations of Kalimantan and Sulawesi were concentrated in discrete areas, primarily along the coast. Communication between these population centres was much more difficult than in Java or Sumatra. In effect, they were more like a series of comparatively small island populations than a land mass over which travel was easily accomplished. Many outbreaks undoubtedly terminated spontaneously and others responded to comparatively perfunctory containment and vaccination activities, as was the case in much of Africa, for example. After transmission had been interrupted in an area, smallpox was reintroduced only infrequently.

Table 13.18. Kalimantan and Sulawesi[a]: percentage of children unprotected by vaccination, by age group, February 1974

Province	Population (thousands)	Number surveyed	Percentage unprotected in age group (years):			
			0–1	1–4	5–14	0–14
West Kalimantan	2 084	3 403	87	60	20	42
Central Kalimantan	643	3 173	81	44	18	35
South Kalimantan	1 907	3 154	84	57	26	45
East Kalimantan	714	3 321	79	43	22	35
Central Sulawesi	865	3 989	73	39	12	30
North Sulawesi	1 710	6 880	72	36	16	34
South-east Sulawesi	716	3 618	68	30	8	26

[a] South Sulawesi excepted.

INDONESIA'S LAST OUTBREAK, 1971

After the last cases occurred in Sulawesi in November 1971, 4 weeks elapsed during which no smallpox cases were reported in Indonesia. It appeared that transmission had been interrupted, but on 14 December 1971, the Director of the Smallpox Eradication Programme received a report from Tangerang Regency (one of the 24 regencies/municipalities in West Java) of 45 cases and 6 deaths in Sepatan Subdistrict, only 28 kilometres from Jakarta. Tangerang (population, 1 million) had recorded its last cases in February 1971, fully 10 months earlier. A village-by-village search had been conducted in West Java between June and August 1971 in the subdistricts which had reported cases during 1970–1971; lack of personnel had precluded a search in all subdistricts. Sepatan Subdistrict had not reported cases during this period and thus had not been searched.

On investigation, it was found that as early as December 1970, a whole year earlier, many cases in Sepatan had begun to be reported to the health centre by the subdistrict's vaccinator. The medical officer of the health centre periodically organized ineffectual mass vaccination campaigns to control the outbreaks but deliberately suppressed the reports of smallpox, fearing that he might be punished for incompetence. In mid-December 1971, a provincial mobile surveillance and supervisory team visited the area on routine tour and was informed of the outbreaks by the local staff (Cuboni et al. in WHO/SE/76.85).

Search and containment activities were immediately instituted. In the realization that the suppression of reports might be widely prevalent, the decision was made to offer a transistor radio to any person who reported an active case of smallpox. This, so far as is known, was the first occasion in the Intensified Programme when a reward was offered for case reporting. It proved to be highly effective. Numerous suspected cases with illnesses of all types were reported by people throughout the area. Eventually, 160 smallpox cases with 15 deaths were confirmed in 3 villages (total population, 7982) of Sepatan Subdistrict; nearly one-third were unprotected when containment vaccination had begun (Table 13.19).

The outbreak had started in Sarakan village in December 1970 (Fig. 13.10), 1 year previously, as a result of an importation from West Jakarta. Smallpox spread slowly, only 14 cases occurring between December 1970 and May 1971. Eventually, the outbreak was contained by a local vaccinator. Meanwhile the disease had spread to Sangiang village in May 1971 and, in September, numerous cases began

Table 13.19. Sangiang, Sarakan and Gaga villages, Sepatan Subdistrict: number of vaccinations performed during containment operations, 1972

Village	Population	Number of vaccinations			Percentage unprotected[a]	Number of cases
		Primary vaccination	Revaccination	Total		
Sangiang	3 106	1 142	2 013	3 155	36	131
Sarakan	1 904	307	1 371	1 678	18	17
Gaga	2 972	917	1 627	2 544	36	12

[a] I.e., those receiving primary vaccination as a percentage of the total vaccinated during the containment phase.

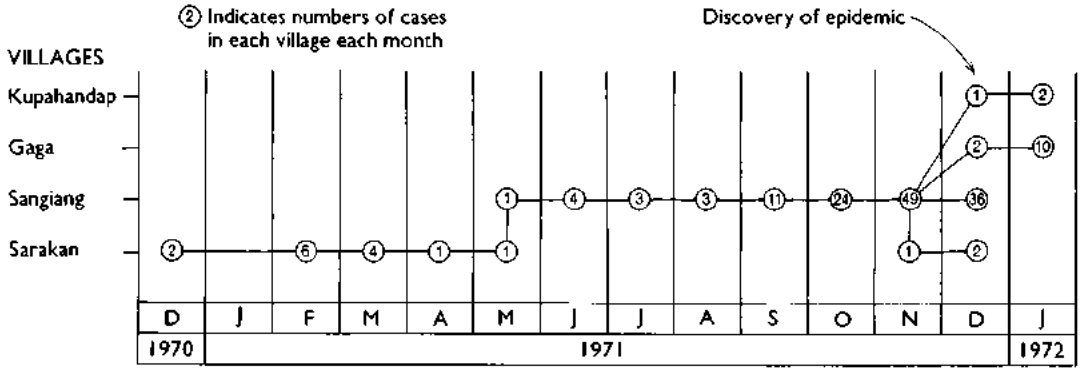


Fig. 13.10 Indonesia: last chain of smallpox transmission, 1970–1972.

to occur. In all, 131 persons eventually developed smallpox in this village of 3106 persons. At the end of November the disease was reintroduced into Sarakan village and, in December, it spread to nearby Gaga village. Finally, late in December, an outbreak of cases developed in a village 80 kilometres distant. The last 2 known cases in Indonesia occurred on 23 January 1972, one of them in Gaga village, and the other in Kupahandap village.

Concerned that other hidden foci might be present elsewhere in Indonesia, the programme staff decided in May 1972 to offer a reward of 5000 rupiah (US$12) to anyone reporting a case. This was widely publicized. The following month, teams from throughout Indonesia began an active search programme. Numerous rumours were investigated and many specimens were examined, but no further cases were found. A summary of the numbers of specimens examined in laboratories during 1969–1973 (Table 13.20) indicates the extent of this activity.

MORBIDITY AND MORTALITY PATTERNS

Smallpox in Indonesia exhibited two unusual features: (1) an exceptionally large proportion of cases among younger children; and (2) case-fatality rates which were often lower than those observed elsewhere in Asia.

In June 1969 the Joint WHO–Indonesia Assessment Team analysed the age distribution of 3823 cases in selected areas and during periods when reporting was considered to be reasonably complete (Table 13.21). The age distributions were similar in West and Central Java and Jakarta, in which smallpox was then endemic. Cases in East Java occurred primarily in outbreaks following importations and the patients were generally older, as was the case in other non-endemic areas. Excluding the data for East Java, 68% of cases occurred in children aged 0–4 years, a group which comprised only 18% of the population of the country. A surprisingly high incidence—about 12%—was found in infants under 1 year of age, twice the proportion recorded in India.

Smallpox spread in Indonesia more readily than in most parts of the world and transmission occurred throughout the year with no apparent seasonal pattern. The facility of spread can be attributed to the high population density and the custom in Indonesia of carrying sick children to visit relatives, thus exposing many more susceptible individuals.

The reported case-fatality rates in many years and during most outbreaks appeared to be lower than those in the Indian subcontinent. This is the converse of what might have been expected, because cases in Indonesia were proportionately more numerous in the very young, among whom case-fatality rates are customarily higher. The question whether case-fatality rates in Indonesia were substantially and uniformly lower than those in the Indian subcontinent was never resolved. The reporting of both cases and deaths was grossly incomplete throughout Indonesia before 1968. The degree of underreporting of cases compared to that of deaths undoubtedly differed from year to year. This probably accounted for such discrepancies as a case-fatality rate of 10% in 1950 and one of 44% only a year later. With the commencement of the national programme, the reporting of cases gradually improved, more rapid pro-

Table 13.20. Indonesia: laboratory examination of specimens, 1969–1973

Year	Number of regencies submitting specimens	Number of specimens	Number positive for variola virus	Number positive for vaccinia virus
1969	19	235	74	0
1970	37	250	55	0
1971	38	150	15	0
1972	113	1 009	12	1
1973	109	599	0	6

gress being achieved in some areas than in others. However, as in other countries, few efforts were made to improve the completeness of the notification of deaths. Since the programme's goal was to interrupt the transmission of smallpox, it was more important to know where and how many cases were occurring than to be aware of how many deaths had taken place.

In containing outbreaks, especially in 1970–1971, the smallpox eradication staff carefully enumerated cases, and because teams remained in the infected areas, the numbers of deaths (which usually occurred 1–2 weeks after the onset of illness) were also known fairly accurately. In those outbreaks, case-fatality rates of 5–10% were often observed, about half as high as the rates in the Indian subcontinent. Data from Jakarta, however (Fig. 13.11), consistently showed much higher case-fatality rates. Jakarta had had a reasonably complete system for the notification of deaths since 1965 and for the reporting of cases since 1968. The case-fatality rates were twice as high as those of West Java, a province which surrounds it and across whose borders residents moved freely. In other respects, the populations were essentially similar with regard to nutrition and general health. If it is assumed that the virus strain in Jakarta was the same as that in West Java, the obvious explanation for the lower rates in West Java would be incomplete notification of deaths. And yet the case-fatality rates in West Java were similar to those observed later in some well-studied outbreaks elsewhere in Indonesia. The observations were never reconciled.

CONCLUSIONS

Smallpox transmission in Indonesia was interrupted just 3 years and 7 months after the programme began in July 1968. This was a remarkable achievement considering the country's size, population and the limited international resources provided. The experience in Indonesia had a profound effect on other programmes during the succeeding years. Among the innovations were the WHO smallpox recognition card, the offer of a reward for reporting a case, a procedure for the systematic search for cases throughout a wide area, and the demonstration of the efficacy of a search based on contact with teachers and schoolchildren. More important, the success of the surveillance–containment strategy was forcefully communicated by Indonesian programme staff to their counterparts in the Indian subcontinent through papers and seminars. Of particular significance was a specially convened WHO interregional seminar in New Delhi in December 1970. One of the papers, contributed by Dr Koswara, the Indonesian programme's director (Koswara in WHO/SE/71.30), was

Table 13.21. Java: age distribution of 3823 cases of smallpox, 1968–1969[a]

Age group (years)	Province							
	West Java		Central Java		East Java		Jakarta	
	Number	%	Number	%	Number	%	Number	%
<1	184	13	103	11	15	7	166	13
1–4	575	40	455	49	84	38	599	48
5–14	496	35	278	30	62	28	263	21
⩾15	173	12	98	10	59	27	213	17
Total	1 428	100	934	100	220	100	1 241	100

[a] Includes only cases, from parts of regencies and for limited periods, whose precise age was known.

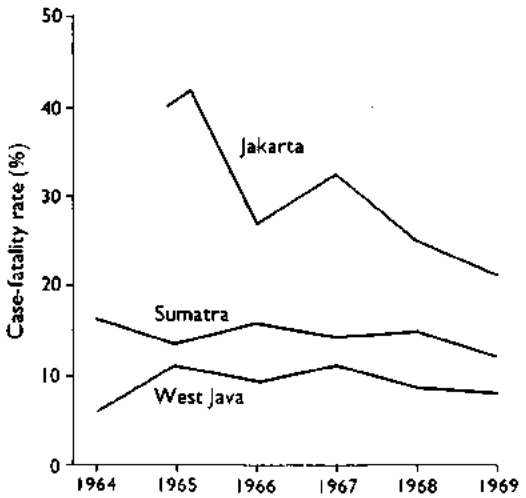


Fig. 13.11. Jakarta, Sumatra and West Java: smallpox case-fatality rates, 1964–1969.

entitled: "Is Routine Vaccination a Necessity in a Smallpox Eradication Programme?" The author concluded that proper surveillance–containment action had brought smallpox under control in a short period, while routine vaccination and mass vaccination campaigns had had little effect in interrupting transmission. Many participants at the conference severely criticized this view, which they considered tantamount to heresy. At that time, Indonesia had not yet stopped transmission in Java, let alone in Sumatra or Sulawesi. Because of this, few of the participants were persuaded by Dr Koswara's arguments. However, with the occurrence of Indonesia's last case in January 1972, it was apparent that the 11-year-old programmes in India and Pakistan had much to learn from the Indonesian experience. A strong stimulus for change was provided.

Plate 13.8. Misah Bin Inang (**A**), one of the last two smallpox patients in Indonesia, became ill on 23 January 1972. Facial pockmarks are apparent in this picture taken in 1979, but many persons (**B**) were more severely afflicted.

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CHAPTER 14

AFGHANISTAN AND PAKISTAN

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INTRODUCTION

In 1967, endemic smallpox in continental southern Asia extended over a contiguous block of countries from Afghanistan through West Pakistan, India, Nepal, Bhutan, and East Pakistan. Epidemiologically, this area could be subdivided into two parts: a western part consisting of Afghanistan and West Pakistan and an eastern part that included India, Bhutan, Nepal and East Pakistan. Separating these two parts was the heavily guarded border between India and West Pakistan. Few persons travelled across this border and, so far as is known, no cases of smallpox were imported across it after 1966. The health programme of West Pakistan functioned quite independently of that of East Pakistan, and in December 1971, when the latter province became the independent state of Bangladesh the two programmes were, of course, entirely separate. The programme in East Pakistan/Bangladesh is described in Chapter 16 and the programmes in India, Bhutan and Nepal in Chapter 15.

West Pakistan and Afghanistan were epidemiologically closely linked because numerous travellers moved freely across their long common border (Fig. 14.1), including several hundred thousand nomads who lived in Pakistan in the winter and in Afghanistan in the summer. Smallpox spread easily across this border.

Pakistan and Afghanistan are both Muslim countries but differ greatly in most other respects—politically and geographically, in historical and socio-economic development and in the manner in which their smallpox

Fig. 14.1. Afghanistan and Pakistan and adjacent countries.

eradication programmes evolved. A WHO-assisted vaccination campaign had begun in 1963 in Afghanistan. By 1967, encouraging reports from programme staff made it seem reasonable to expect that systematic vaccination in the towns and cities and a national outbreak-containment programme would rapidly interrupt transmission. This optimistic view faded a year later, when it was discovered that itinerant hereditary variolators were active throughout much of the country, particularly in the extensive remote mountainous areas, spreading smallpox as they travelled. Because Afghanistan was a country with few roads, a primitive health infrastructure and orthodox religious practices which impeded vaccination, it was feared that transmission might be sustained in isolated, virtually inaccessible areas despite the best efforts at control. As late as 1971, WHO senior staff believed that Afghanistan might be the endemic country most likely to thwart the ultimate goal of global eradication. An extraordinary programme and a heroic effort by Afghan and WHO staff were to produce yet another surprise when, in September 1972, Afghanistan succeeded in interrupting smallpox transmission.

Pakistan, in contrast to Afghanistan, had a comparatively well developed health infrastructure, extending throughout most of the country, and a population which generally could be easily reached by the relatively extensive network of roads. A programme of routine smallpox vaccination had been established since the late 19th century; variolation was rarely practised. The epidemiological behaviour of smallpox in Pakistan had been characterized during 1966–1967 in a unique series of studies whose findings were to prove significant in shaping the strategy of eradication programmes in other countries. An important observation was that urban centres played a crucial role in sustaining smallpox transmission, especially during the summer and autumn, when the incidence was low. The investigators discovered, however, that even during the months of highest incidence and in what was considered to be a heavily infected district, the number of outbreaks was sufficiently small to require only a few teams to detect and contain them. Because they found the levels of vaccinial immunity to be already high in Pakistan, the investigators recommended that priority should be given to detecting and containing outbreaks, especially in urban areas and during the season of lowest incidence. Paradoxically, however, Pakistan was among the last countries to adopt a strategy based on these recommendations. Until 1973, national and WHO programme staff persisted in executing a mass vaccination campaign which was indifferently supported and not satisfactorily conducted. Despite the many factors favouring smallpox eradication, transmission was not interrupted in Pakistan until October 1974.

Meanwhile, there was little communication and virtually no coordination of activities between the programmes in the two countries. Numerous cases of smallpox were imported into Afghanistan from Pakistan and special surveillance programmes had to be developed to combat the threat they represented, which became all the more serious when Afghanistan succeeded in interrupting transmission more than 2 years earlier than Pakistan. The two programmes differed greatly and are discussed separately in this chapter.

AFGHANISTAN

Few of the endemic countries posed as many difficult and unusual challenges as did Afghanistan. In 1967, this isolated, landlocked country was in an early stage of economic and institutional development. The government structure was rudimentary, and in some remote areas the central authority was

not recognized. The population—90% of which was illiterate—is estimated to have been 11.9 million in 1968 (United Nations, 1985), although no census had ever been taken.

The Hindu Kush mountain range, with peaks as high as 7500 metres, extends from the extreme north-east border with China towards the south-west, much of central Afghanistan having an altitude of more than 2000 metres (Fig. 14.2). Because of snow, this area was largely inaccessible for almost half the year. The south-western part of the country is mainly desert, where the extreme heat precluded most programme activities during summer. Except for a single paved all-weather road that circled the country, with occasional branches to provincial capitals, the roads were extremely poor, challenging even heavy-duty vehicles. There were no navigable rivers, no railway, and only limited air connections. Programme operations and efforts to communicate with the population were hampered by illiteracy and by the use of 3 different major languages—Dari, Pushtu and Uzbeki.

Most of the population lived in the 20 000 villages in rural areas and less than 15% in the main cities of Kabul, Kandahar, Herat and Mazar-i-Sharif. Religious practices were strict among the predominantly orthodox Sunni Muslim rural dwellers, and religious leaders were highly influential. Of importance to smallpox eradication was the observance of purdah, whereby women were secluded within their homes and the male heads of household refused to permit them to leave the house for vaccination or to be vaccinated by male vaccinators.

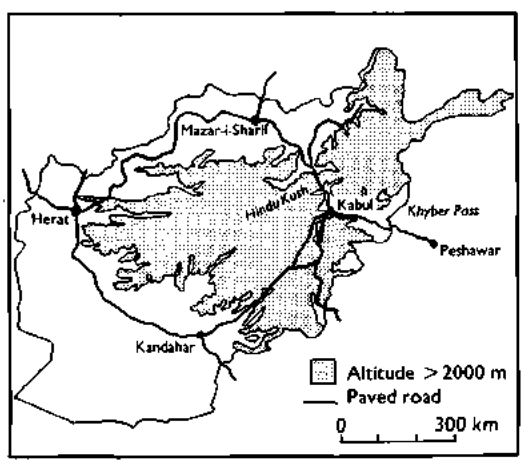


Fig. 14.2. Afghanistan: topography and principal roads.

The health structure was rudimentary. In 1965, there were reported to be 19 primary health centres and 60 hospital-clinics staffed by physicians who were responsible for both curative and preventive services, although few offered even the most elementary preventive measures (World Health Organization, 1965b).

Smallpox Control before 1963

For centuries, variolation had been practised throughout Afghanistan by traditional variolators, the technique usually being communicated from father to son. Many variolators travelled considerable distances in the course of their work. A fee of 10–15 afghanis (US$0.15–0.20) was the usual charge. Scabs (rarely pustular material) from a patient were collected and ground with a mortar and pestle, and the powder suspended in a liquid. The suspension was inoculated by scratch or by pinprick on the forearm or near the wrist. Variolators usually obtained fresh material each year, and therefore variolation tended to be performed during the autumn and winter months, after the number of cases had begun to increase.

Vaccination was all but unknown in Afghanistan until 1936, when a campaign was organized that succeeded in vaccinating 3 million persons over a 3-year period; liquid vaccine produced at a laboratory in Kabul was used (Berke, 1956). This laboratory continued to produce small amounts of vaccine which, during subsequent years, was primarily used in and around Kabul. Because the vaccine was of questionable potency, as well as being thermolabile, vaccinial immunity in 1967 was probably not high, even in Kabul.

In 1949, Afghanistan began to keep records of the number of cases of smallpox. Between 1949 and 1968, the annual total ranged from a low of 66 cases in 1966 to a high of 2179 cases in 1952. However, the figures had little meaning since the only cases reported were those which were diagnosed in the country's few health centres. A simple calculation provides an approximation of the probable extent of underreporting. In a population of 10 million, each year about 300 000 would survive the perinatal period to constitute a new group of susceptible subjects. Because

Plate 14.1. For hundreds of years, variolation had been widely practised throughout Afghanistan by hereditary variolators using kits such as these. Scabs were collected from a recovering patient and kept in a container such as a metal box (**A**) or horn (**B**). Before inoculation, the dried scabs were ground up, usually in a primitive mortar and pestle (**B**). A liquid such as honey or water with spices was added and a drop of the suspension was applied to the skin. This was then inoculated into the superficial layers of the skin, using a needle or lancet. Sometimes a special strip of cloth (**B**) was used, and reused repeatedly, to bind the site of the incision until a pustule formed.

few individuals were successfully vaccinated, almost all would eventually become infected with smallpox. Thus, on average, 300 000 persons would experience smallpox each year, either by natural infection or as a result of variolation—i.e., more than 350 times the average of 840 cases reported annually between 1949 and 1963.

Commencement of a WHO-assisted Vaccination Campaign, 1963

Following the Twelfth World Health Assembly's resolution in 1959 to embark on the global eradication of smallpox, Afghanistan sought and obtained assistance from WHO to begin a special campaign. It was one of only a few countries to receive technical and material support from WHO for field activities in smallpox eradication during the period 1959–1966. A WHO adviser was assigned to Kabul in 1962; in March 1963, a vaccination campaign began in the capital. During the following year, the campaign was extended to 9 provinces (World Health Organization, 1965b). Freeze-dried vaccine provided by the USSR and locally produced liquid vaccine were used. By the end of June 1964, 392 026 of the 400 000 residents of Kabul were reported to have been vaccinated by a staff of 139 male vaccinators and 7 female vaccinators and auxiliary midwives. Twenty-five of the vaccinators were then kept in Kabul "to carry on the maintenance phase and to fight epidemics", as the WHO adviser reported. The remainder were assigned to the provinces to work under the direction of provincial medical officers. Although large numbers of people were subsequently reported to have been vaccinated, the reports were thought to be greatly exaggerated.

In 1965, 3 additional groups, each composed of 70 vaccinators, were trained and dispatched to Kandahar, Ghazni, Wardak and Bamian Provinces (see Fig. 14.3). Young physicians, conscripted for government service, were assigned to supervise each group but few were willing to leave Kabul. What was achieved is unknown because no records were kept.

During the following 3 years, additional resources were provided by WHO, but little progress was made. At the end of 1968, the uncoordinated and poorly supervised series of activities could scarcely be characterized as a programme. The physician in charge of smallpox eradication was also responsible for all the country's communicable disease control activities and could therefore devote little time to the smallpox eradication programme. Young medical graduates, carrying out their compulsory service, continued to be assigned to provide direction but few spent more than a month or two in the field before arranging to be transferred. In the staff hierarchy there were only a few sanitarians between the programme director and the vaccinators, and the turnover among them was almost equal to that of the physicians. The problems were further compounded by inadequate government funds and a complicated financial system which typically resulted in delays of 3 months or more in the payment of salaries and, frequently, a lack of funds to purchase petrol. Within the government structure, the execution of even simple tasks was time-consuming. For any purchase, for instance, 3 responsible individuals were required to visit the bazaar to bargain, to obtain a receipt for the purchase, and then to report to an administrative section where the transaction could be recorded.

The support provided by WHO contributed little. The WHO smallpox adviser devoted most of his time to the preparation of letters advising his Afghan counterpart as to what should be done and to the compilation of monthly reports. He rarely travelled out of Kabul. Two WHO nurses, assigned to the programme in 1967, likewise travelled little and, although sharing an office with the adviser, received most communications from him in the form of typed memoranda. Eighteen vehicles had been provided to the programme of which 9 were not sufficiently roadworthy to leave Kabul and 7 had been coopted for the use of various officials in the Ministry of Health.

In April 1968, a medical officer responsible for smallpox eradication in the WHO Regional Office for South-East Asia reported in despair that no one knew where the provincial vaccinators were stationed or what they were doing. No records were kept, in part because most of the vaccinators were illiterate. The group of vaccinators in Kabul was periodically dispatched to the field when a report of an outbreak was received. They travelled in a large flatbed truck to the site with orders to vaccinate everyone in the area. After some days or weeks had elapsed, they gradually filtered back to Kabul. No report was prepared on what had been accomplished.

Meanwhile, the USA had been approached by the Afghan government and asked to send female volunteers to assist in vaccinating women throughout Afghanistan. Women, it was said, could not be vaccinated by male vaccinators nor could they leave their dwellings in most areas. The volunteers would be expected to work with Afghan women counterparts as members of teams vaccinating from house to house. The concept was attractive but unrealistic. A small contingent of United States volunteers could themselves vaccinate no more than a fraction of the population, and given the religious strictures of the country, the recruitment of Afghan women was all but impossible.

The unsatisfactory vaccine then being used presented no less of a problem. Although liquid vaccine production had ceased in Kabul, the freeze-dried vaccine provided through bilateral assistance did not meet accepted standards, as was attested by protocols provided by the production laboratory itself. Moreover, all vaccine was then being stored at room temperature, which caused it to deteriorate even further.

Finally, the scope of the smallpox problem itself was not comprehended. Early in 1967, the WHO adviser, noting that only 72 cases had been reported in 1965 and 66 cases in 1966, confidently estimated that in the entire country there probably were not more than 300 cases each year, most of them in children. If indeed there were so few cases, it could be inferred that there were comparatively few chains of transmission. Geneva staff, who were ignorant at that time of the moribund state of the programme, hopefully proposed an alternative strategy to country-wide vaccination: (1) intensive containment of known outbreaks by special teams; and (2) a programme of primary vaccination of children in the cities and towns. This, it was felt, might serve to concentrate resources in priority areas and alleviate the problem of supervising vaccinators so widely dispersed over the countryside. No action was taken, however.

When Henderson and Dr Jacobus Keja, of the WHO intercountry team advising on smallpox eradication, visited Afghanistan in October 1968, the full array of problems became apparent. Not only did they discover that the programme existed in name only, but they found that conditions in Afghanistan differed substantially from the situation described in reports and were far more serious than had hitherto been thought. Even with the woefully inadequate notification system, 334 cases were recorded in 1967 and 739 in 1968. Smallpox was far more widespread than had been supposed. Variolation was found to be common and some, perhaps many, of the outbreaks resulted from this practice. The fact that variolators were most active in the least accessible parts of the country was of particular concern. They retained infected scabs for 1–2 years and travelled considerable distances to perform inoculations. Moreover, because the government had begun to discourage the practice, villagers usually refused to identify the variolators, fearing that they would be punished. On the basis of these observations, it was suspected that smallpox transmission, perpetuated by variolation, might persist indefinitely among a remote, comparatively small population of susceptible persons. The optimistic outlook in 1967 that Afghanistan might soon interrupt transmission gave way towards the end of 1968 to fear that the country might prove to be the world's last and possibly permanent reservoir of smallpox.

The previously suggested strategy of vaccinating the more accessible members of the population, coupled with the search for cases and the containment of outbreaks, could not solve the problem caused by variolation. Special efforts would be needed to educate villagers about the hazards of variolation and to identify variolators and persuade them to stop their practice. It was recognized, however, that such efforts would be only partially successful because the identity of variolators was kept secret. Other measures were required. The only possible approach, apart from outbreak containment, appeared to be that of vaccination of the population at large to diminish the number of susceptible individuals available to variolators as clients and as a source of scabs. This would be particularly important in the remote areas in which variolation was most prevalent. Meanwhile, special efforts would be required to characterize epidemiologically all outbreaks so as to uncover evidence of variolation. Considering the poor record of achievement of the programme during the 6 years 1963–1968 the task appeared formidable, perhaps impossible.

Changes in the Strategy and Structure of the Eradication Programme, January 1969

During extended discussions between government officials and Henderson and Dr

Keja, a new plan of operations was formulated. The key Afghan officials who provided the essential impetus in the design and implementation of the programme were the perceptive and energetic Dr Sayed M. Saidi, President of Preventive Medicine, and Dr A. Omar, Deputy Minister of Health. An agreement was signed by the government on 12 December 1968 and by WHO 3 weeks later. The plan called for the appointment of a full-time Afghan medical director who was to be given sufficient authority and responsibility to direct the programme and the establishment of 4 operational zones (Fig. 14.3)—Kabul, Kandahar, Kunduz and Herat—with a zone office in each. A full-time medical officer and 3 sanitarians, assisted by a WHO adviser, would be assigned to each office. Each zone director was to be delegated full responsibility for the programme in his zone, with authority to discipline personnel and to recruit and train replacements, to requisition fuel for transport and pay for repair and maintenance, and to make all necessary travel arrangements for staff within the zone. Although the recommendations were administratively sound, such responsibilities had not previously been assigned to supervisory staff outside Kabul. Despite a conscientious effort to achieve the requisite delegation of authority, the lack of decentralized authority plagued the programme throughout its existence.

Personnel needs were identified and a budget was drawn up (Table 14.1). With only 4 motor vehicles and 6 motorcycles then available, it was recognized that the programme could not become fully operational until at least August 1969, when the delivery of an additional 44 vehicles, provided by WHO, was expected. Each province was allotted 1 vehicle each for the zone director, the WHO adviser, an outbreak-containment team and an assessment team, and 5 vehicles for the vaccination teams. Other vehicles were to be kept in reserve.

The plan called for vaccination teams to move systematically from village to village

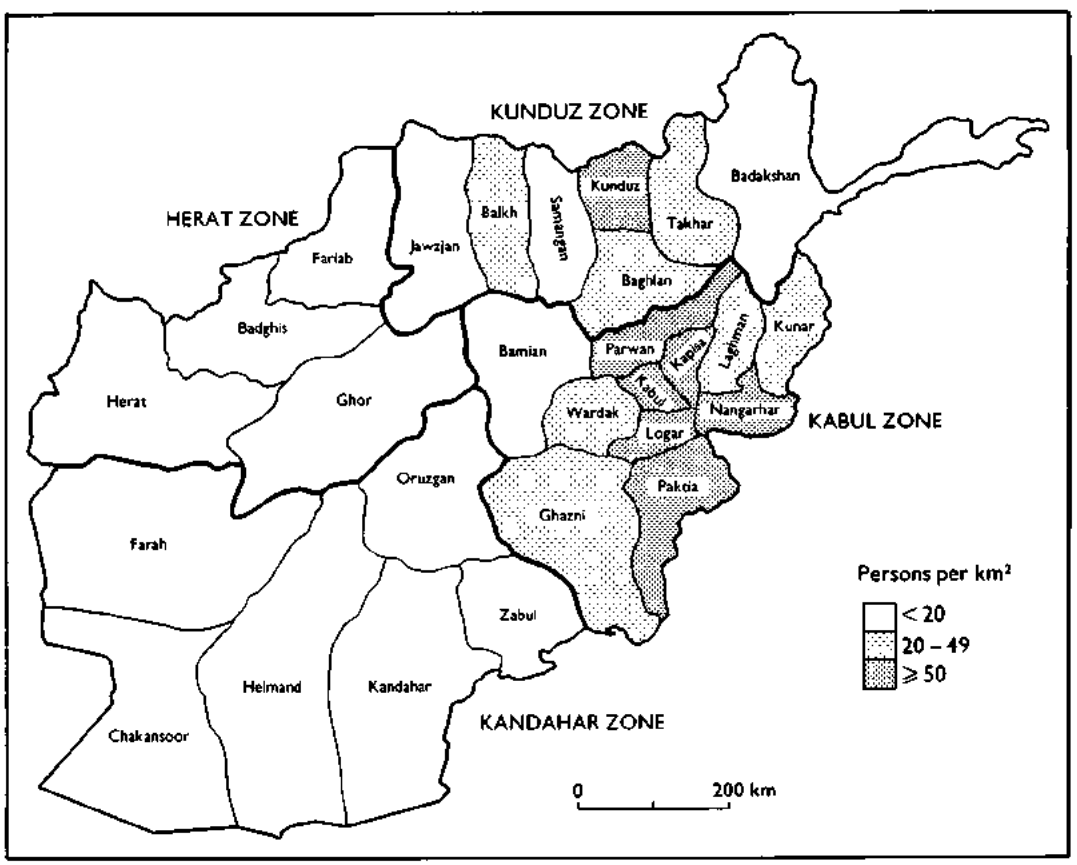


Fig. 14.3. Afghanistan: operational zones established for smallpox eradication, and population density by province, 1969.

Table 14.1. Afghanistan: budget for the smallpox eradication project, 1969[a]

	Number	Expenditure (afghanis[b])
Personnel		
Medical officers	5	234 000
Sanitary inspectors	14	239 400
Vaccinators	223	3 007 940
Drivers	37	599 400
Office staff	15	148 240
Total		4 228 980
Other items		
Petrol and oil		64 000
Repairs		20 000
Office rent and furniture		69 000
Miscellaneous		48 000
Total		201 000
Grand total		4 429 980

[a] For the Afghan year 1348 (21 March 1969–20 March 1970).
[b] 10 afghanis were worth approximately US$0.15. The total national budget was thus equivalent to about US$66 500.

Table 14.2. Afghanistan: WHO support to the smallpox eradication programme, 1964–1977[a] (US$)

Year	Personnel, training, local costs	Supplies, equipment and other items	Total
1964	15 515	–	15 515
1965	18 069	–	18 069
1966	15 313	–	15 313
1967	28 248	–	28 248
1968	38 220	142 622	180 842
1969	100 057	4 186	104 243
1970	85 478	49 477	134 955
1971	135 219	16 209	151 428
1972	147 356	6 509	153 865
1973	168 200	4 936	173 136
1974	146 816	8 504	155 320
1975	125 320	102	125 422
1976	140 930	–	140 930
1977	58 247	–	58 247
Total	1 222 988	232 545	1 455 533

[a] Excluding supplies of vaccine.

and from house to house, preceded 3–10 days earlier by a visit of the team's leader to inform village leaders of the programme and to instruct them about the hazards of variolation. Instead of the name of each vaccinated person being recorded, vaccinations would be tabulated by age group on a tally sheet. An assessment team would visit a sample of children in the villages 1–3 weeks later to assess vaccination status, take rates following vaccination and the prevalence of variolation scars. Surveillance–containment teams would visit civil and health authorities in their respective zones to seek cooperation in reporting and to investigate and contain outbreaks.

In addition to miscellaneous supplies such as refrigerators and office equipment, WHO agreed to provide up to 4 million afghanis (about US$60 000) each year for travel allowances for headquarters and zone staff and for petrol and vehicle maintenance and repairs. Eventually WHO provided Afghanistan with more than US$1.4 million in support of the programme (Table 14.2), an amount equivalent to about US$0.12 per head of population. In addition, freeze-dried vaccine was provided by the USSR and from contributions received by WHO.

In February 1969, Dr A. G. Rangaraj, a newly recruited senior WHO adviser on smallpox eradication, joined the programme, replacing the previous incumbent. Dr Rangaraj had served with distinction in the Indian Army Medical Service and brought to the programme a unique expertise and capability in programme organization and logistics. With the 2 WHO nurses already assigned, Miss Khin Mu Aye and Miss Ludmila Chicherukina, and later an additional epidemiologist, Dr V. V. Fedorov, an exceptionally effective WHO advisory team was created. In May 1969, the Afghan goverment appointed a no less determined and energetic full-time programme director, Dr Abdul Mohammad Darmanger, who ably fulfilled this role for the next 5 years.

Establishment of zone offices and effective field activities

Most of the Afghan smallpox eradication programme staff lived in Kabul, and the attractions of urban life discouraged prolonged work in the field. It was felt that a second base of operations, outside Kabul, with staff recruited from the local area, would facilitate field work. An office-cum-dormitory was rented in Kandahar and some work began from this base as early as November 1968. The staff initially consisted of an Afghan medical officer as director, 6 sanitarians, 44 vaccinators, 3 drivers, a cleaner, several volunteers from the USA and the 2 WHO nurses. Work was frequently interrupted, however, because of numerous national and religious holidays and periodic strikes by Afghan staff when they failed to receive salary or travel allowances because of the complicated payment system. Another hindrance was the frequent change of zone medical

Plate 14.2. **A**: Sayed M. Saidi (1923–1970), President of Preventive Medicine in the Ministry of Health of Afghanistan, provided a new impetus to the programme in 1968. **B**: Arcot G. Rangaraj (b. 1917) became the senior WHO adviser on smallpox eradication in Afghanistan in 1969 and, with Abdul Mohammad Darmanger, his Afghani counterpart, directed Afghanistan's first, and highly effective, nation-wide health programme. He later served with the smallpox eradication programmes in Bangladesh and in the Arabian peninsula.

directors (3 in the first 8 months alone), few of whom were anxious to undertake field work, or to live outside Kabul. Nevertheless, by June 1969, almost the whole population (742 000) of Kandahar, the largest province in the zone, had been vaccinated. Assessment showed that more than 90% of the population had been protected.

It became apparent during this period that, contrary to previous ideas, the 30 United States women volunteers were not essential to the work of vaccination. It was found that when village leaders were properly informed about the nature of the programme, women were usually permitted to be vaccinated by male vaccinators, although sometimes on the forearm or wrist rather than on the upper arm, the customary site of vaccination. From the investigation of outbreaks, it also became apparent that few cases occurred among women, most of whom by the age of puberty had experienced smallpox or had been variolated or vaccinated. Thus, even if some were missed during the vaccination campaign, only a small proportion would remain susceptible. Accordingly, the volunteers were reassigned to assessment and surveillance teams and some helped to establish the necessary administrative and support structure at headquarters and zone offices. They were a dedicated group and made important contributions to establishing the new programme, but when any of them left they were not replaced. Their number had dwindled to 9 by 1970 and to only 1 by 1971.

In July 1969, a third office was established in Baghlan Province, for Kunduz zone, with 2 team leaders, 2 sanitarians and 17 vaccinators. One of the WHO nurses was transferred to Baghlan and several United States volunteers were deputed to work in this office.

Not unexpectedly, a reorganization and reorientation of activities of the magnitude proposed in the plan of operations caused serious difficulties. A joint Afghan–WHO assessment team made an inspection visit in August 1969 and detailed in their report continuing major problems:

- The national programme office had no telephone, secretarial assistance, stationery, files, forms or records. Sanitarians appointed (as administrators) had neither the background nor the skills necessary to discharge their duties.
- The director had no apparent authority—i.e., he had no direct access to a defined budget, no authority either to establish or to enforce personnel policies and no authority to deploy assigned resources (e.g., vehicles, subsistence allowance) without individual written authorization by his immediate superior. Indeed, his superiors appeared to act independently with smallpox eradication programme resources without prior consultation.

- Only 1 team in 5 in Kandahar zone had worked at all from mid-June to early August and then for only 1 week. In August, 13 of the 53 team members in Kandahar had been sent for military service. Field allowances were not being paid nor were funds available for petrol. These factors were responsible for a strike by vaccinators in Kunduz zone.
- The director's lack of authority was illustrated by his inability to dispatch a truck to the airport to pick up a vaccine shipment; this resulted in the vaccine remaining in a hot unventilated shed for 8 days.
- The director had been unable to obtain maps for field operations although the Malaria Institute could do so and tourists could buy them from the Cartographic Institute.
- All teams in Kabul zone had been assigned throughout the summer by Ministry officials to perform cholera vaccination.
- No provincial vaccinators were working with the teams, contrary to prior agreements.
- In Kabul zone, there was no zonal administrative structure and no defined plan of action.
- Vehicles had been out of operation for extended periods and reassigned to other programmes; 2 of 7 large vehicles provided by WHO could not be located, nor could one-third of the motor cycles provided.

The assessment team travelled widely throughout Afghanistan in August 1969, talking with health staff and others and conducting surveys for evidence of pockmarks and vaccination scars. There were encouraging findings. Everyone with whom they spoke reported that variolation had markedly diminished in recent years, and of 4999 persons examined in their survey, only 3 were found who had been variolated within the preceding 3 years. The reporting of cases was known to be incomplete but, despite intensive search, the team could find no cases not already known to the programme staff. In areas in which the systematic vaccination campaign had been completed, only 7% of the population remained unprotected (Table 14.3); variolation scars were found in only 5 out of 363 children under 5 years. Even in areas in which a systematic vaccination campaign had not yet been conducted, almost half of the people had vaccination scars and only 23% were unprotected. In nomadic groups, however, only 25% had vaccination scars, nearly 40% had scars of variolation, and 29% remained fully susceptible. The results were encouraging but, at the same time, they had to be interpreted with reservation. Because of time constraints, the assessment teams conducted their surveys in the more accessible areas. Thus, the data undoubtedly indicated a higher level of protection and less variolation activity than might have been expected in the more remote mountainous areas.

Table 14.3. Afghanistan: results of scar surveys in 13 provinces by the WHO assessment team, by age group, August 1969

Type of scar	% previously infected with vaccinia or variola virus, by age group (years)					
	<1	1–4	5–14	⩾15 (males)	⩾15 (females)	Total
Areas in which systematic vaccination campaign had been completed						
Pockmarks of smallpox	0	1	10	11	11	8
Variolation scars	0	2	5	27	37	16
Vaccination scars	61	91	81	57	44	69
Unprotected	39	6	4	5	7	7
Number examined	84	279	609	337	341	1 650
Areas in which no systematic campaign had yet been conducted						
Pockmarks of smallpox	1	1	5	17	18	10
Variolation scars	0	2	11	31	32	18
Vaccination scars	38	70	71	28	29	49
Unprotected	62	28	14	25	21	23
Number examined	143	512	871	548	815	2 889
Nomadic population (Kuchis)						
Pockmarks of smallpox	0	0	8	14	10	8
Variolation scars	0	8	35	49	63	38
Vaccination scars	16	29	39	18	11	25
Unprotected	84	63	18	20	16	29
Number examined	19	86	137	111	107	460

Many recommendations were made by the assessment team and gradually, over the next 6 months, order began to emerge. The system of payments improved, greater authority was given to the director of the programme and the pace of operations in the zones increased. Nevertheless, zone directors came and went every few months; the turnover of vaccinators remained depressingly high, as they were regularly summoned for military duty or left for other jobs; efforts to utilize the vaccinators assigned to provinces proved futile.

Methodology of the vaccination campaign

The vaccination campaign was simple in concept but required imagination to execute. Five-man vaccination teams moved systematically through the country, completing their task district by district and province by province. The teams worked for a period of 24 consecutive days, followed by 7 days' holiday. The senior supervisor, moving in advance of his team, contacted each district and subdistrict political head and, finally, each village chief to explain what the teams were doing and to solicit their cooperation in ensuring that on the day of the team's visit, the male heads of household would be at home and would agree to let the adult females and children in their household be vaccinated. In most parts of the country, it was possible to vaccinate families only if permission was given by the male heads of household and such vaccination had to be done in the house. The supervisor also explained the hazards of variolation and endeavoured to seek out practising variolators. Variolators, when identified, were sometimes recruited as vaccinators or offered a free supply of vaccine to be used in place of scab material.

A performance goal of 100 vaccinations per vaccinator per day was established. The number was not large, but reasonable considering that many villages could be reached only after hours on foot or horseback, after which each household head had to be individually contacted and his permission obtained to perform vaccination. By the end of 1969, the goal had been achieved by most teams. Initially, the numbers of vaccinations performed were tallied by age group and sex but the vaccinators found it inconvenient to carry paper and pencils and to tally each vaccination performed. A simpler method was adopted. When a team completed work in a village, it simply counted the number of needles used and recorded it, along with the date and the name of the village. The completeness of coverage by age group was determined 1–3 weeks later by an assessment team.

To conduct a systematic vaccination campaign such as this required accurate and detailed maps, but it was soon discovered that the maps provided by the Cartographic Institute and the Malaria Institute omitted many villages and misplaced others. To cope with this problem, the team leader asked each village leader to identify each neighbouring village and its location. These were then added to the map and the map redrawn when necessary.

Methodology for the assessment of vaccination coverage

Assessment of the performance of the vaccination teams played an especially crucial role in the success of the Afghan programme. An assessment team composed of 2 persons visited a 10% sample of the villages 7–10 days after vaccination to determine the proportion of people vaccinated. Assessment was a new concept that was not readily accepted by the national health authorities. It seemed wasteful to them to assign 2 responsible supervisory staff merely to check the performance of others. They argued, moreover, that if assessment was to be carried out, all persons in every village would need to be examined, an impossible task given the limited resources available. Only with difficulty was it possible to persuade the health authorities of the value of a sample assessment which measured the overall performance of a team in a geographical area.

If only some villages were to be visited, which ones should be selected? One approach would have been to use standard statistical sampling methods, which require that every person has an equal chance of being included in the sample. The correct procedure would then have been to take into account the size of the population in each village in drawing the sample. Given the educational level of the staff, this was considered too complex. Another approach would have been simply to ask the teams to assess 10% of the villages in each geographical area. If this had been done, only the most accessible villages would have been checked, and these would have been the villages that the vaccination teams would also have visited. Not only would a falsely high level of vaccination coverage have been

recorded but remote villages in which variolation was prevalent would have been missed. Another scheme was adopted. The name of each village in which vaccination had been performed was written on a piece of paper that was then placed in a box. The assessment team leader drew from the box a number of papers equivalent to 10% of the total, and each of the villages thus selected was then assessed. The process itself was readily understood and it helped to ensure that at least some of the less accessible villages were checked.

To facilitate assessment, a simplified form (Plate 14.3) was developed by Dr Keja and Henderson with the assistance of Mr Svend Brøgger, a WHO statistician assigned to the Public Health Institute in Kabul. It was decided that in each village chosen for assessment, 85 children under 15 years of age and 60 adults should be examined. Children were the more important group, because it was among them that most cases were occurring. They were also the age group more likely to be encountered when the team visited a village. Because adult levels of immunity were found to be consistently higher owing to previous smallpox or to variolation or vaccination, the assessment of adults was later abandoned. The recording form had 145 boxes, 10 for the age group under 1 year, 30 for the age group 1–4 years, 45 for the age group 5–14 years and 60 for the adult group aged 15 years and over, a distribution roughly approximating to the age distribution of village populations.

The assessor was instructed to begin at one end of the village and to proceed house by house until a sufficient number of persons had been examined so that each box would contain a mark. In examining an individual, he looked first at the face. If there were pockmarks, he recorded a "P" in the box and proceeded to examine the next person. If there were no pockmarks, he looked for a variolation scar on the forearm or wrist. If it was present, he marked a "V" in the box. If neither was present, he looked for a vaccination scar and if he found one recorded an "X", or "XX" if it was a primary take. If none of these scars was present, he recorded a "O". He then asked each individual whether he or she had been vaccinated by the team. If the answer was affirmative, a dot was placed within the "O". When assessment was complete, the numbers of different symbols were summed and a simple calculation was performed. Absentees were tallied at the bottom of the sheet; if they were found to be numerous, the assessment was considered invalid. Experience showed that each team could carry out assessments in 2 villages every day.

With this assessment technique, it was possible to determine the immunity level in the village, the proportion of successful vaccinations, the extent of variolation and the past history of smallpox. The work sheet as well as the final report filled up only one side of a sheet of paper. From the physical condition of the report sheet, it was possible to know whether or not the team had actually performed the assessment: a clean form with all symbols neatly inscribed suggested that the data were contrived.

The method of assessment was not what a traditional statistician would have prescribed and the sample was certainly not "statistically valid". However, it was understandable to field staff and provided important information. As such, the sample came to be known as "operationally valid". Eventually, it was adapted for use in many other countries.

Operationally, the goal was established that at least 95% of primary vaccinees should show evidence of a successful vaccination and that not more than 20% of the children under 5 years of age should remain susceptible after a team had vaccinated in a village. Invariably, much higher levels of protection were found among individuals over 5 years of age. Thus, if fewer than 20% of those under 5 years remained susceptible, the overall proportion of susceptible people in the village would be much lower than this, usually less than 10%. If the assessment team found that more than 20% of children under 5 years were susceptible or that the proportion of successful vaccinations was unsatisfactory, the vaccination team was obliged to return to the area to revaccinate the population of all the villages, but its members were not paid a travel allowance. Within months after the assessment teams began work, the proportion of susceptible young children remaining after mass vaccination dropped abruptly from a range of 20–40% to consistently less than 10% and often less than 5%.

Progress in the Vaccination Campaign

Because of the host of administrative problems and the lack of transport, progress in the vaccination campaign remained unsatisfactory during 1969 (Table 14.4). Only

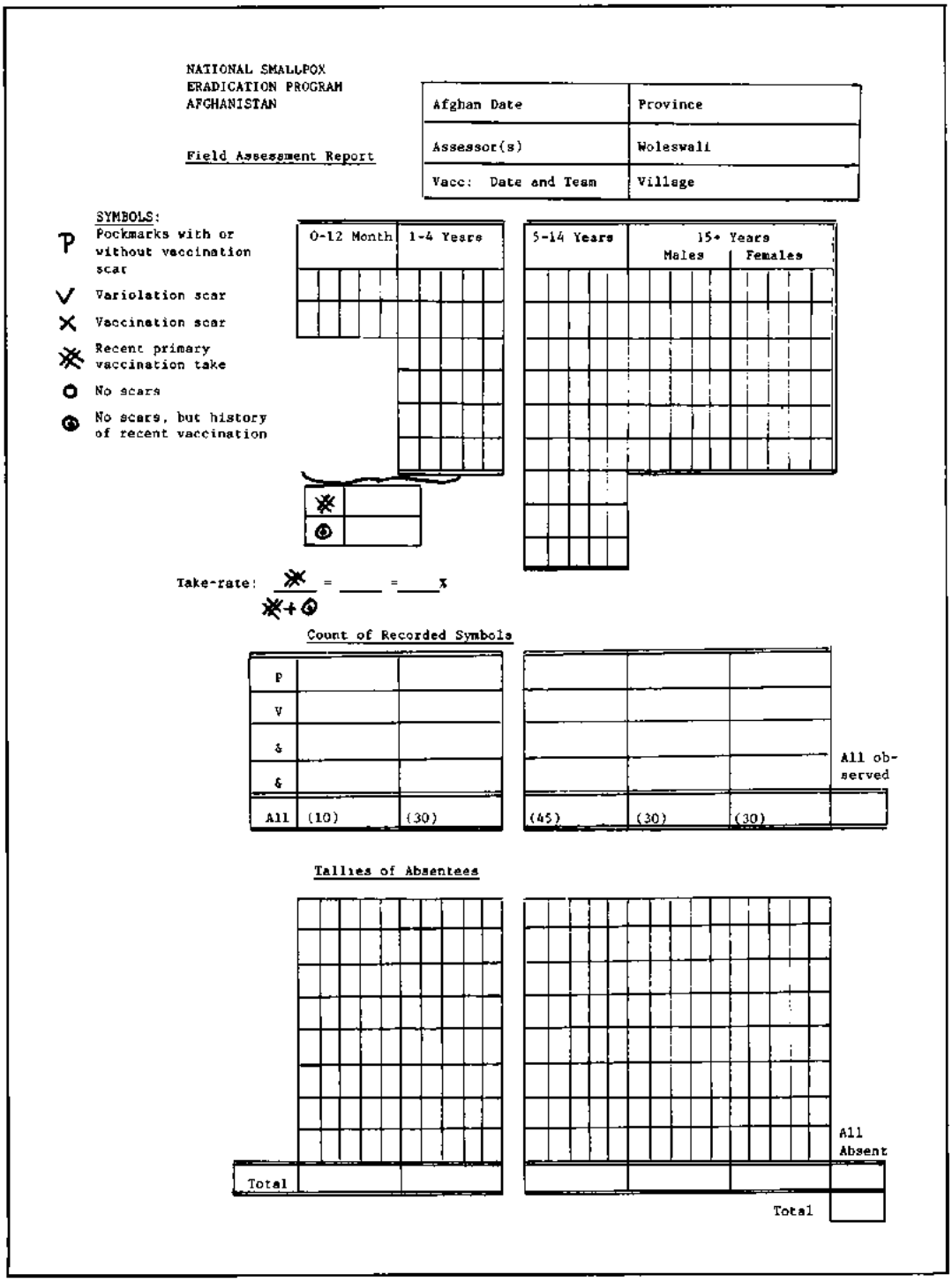


Plate 14.3. Afghanistan: field assessment form, 1969.

545 885 persons were vaccinated during the year, two-thirds of whom were in the Kandahar zone. Vaccination was completed in only 3 provinces (Fig. 14.4). However, as systems improved and operations in the Kunduz and Kabul zones got under way, the pace accelerated. By July 1970, more than 300 000 people were being vaccinated each month. During

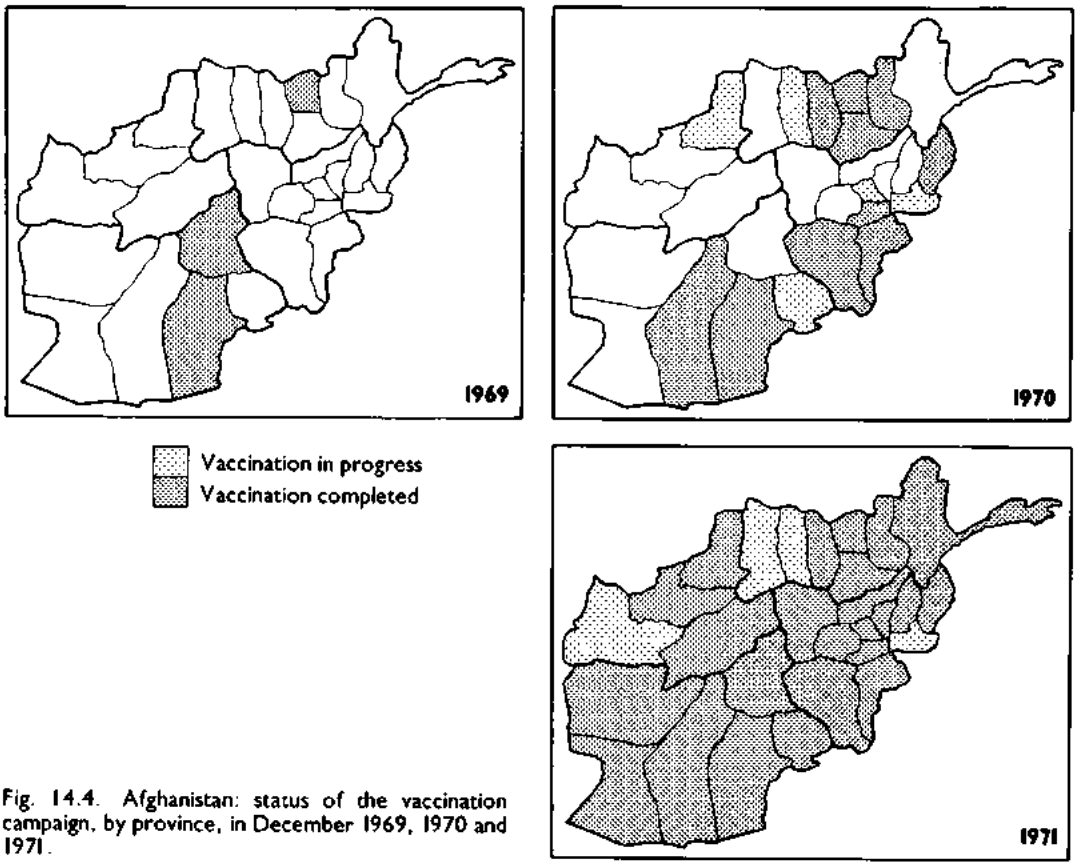


Fig. 14.4. Afghanistan: status of the vaccination campaign, by province, in December 1969, 1970 and 1971.

Table 14.4. Afghanistan: number of smallpox vaccinations in the 4 operational zones, 1969–1974

Year	Total	Kandahar	Kunduz	Kabul	Herat
1969	545 885	333 718	183 167	29 000	0
1970	3 541 643	1 042 013	1 111 090	1 338 540	0
1971	4 676 442	1 193 376	1 342 658	1 671 702	468 706
1972	1 713 237		(Conclusion of first round of vaccination)		
	2 461 797		(Second round of vaccination)		
1973	2 924 921		(Second round of vaccination)		
1974	1 621 774		(Third round of vaccination)		

Table 14.5. Afghanistan: number of programme staff, by category, April 1971

	National medical officers	WHO advisers	Sanitarians	Vaccinators	Drivers	Total
Headquarters	1	1	3	1	1	7
Kabul zone	1	1	8	81	12	103
Kunduz zone	1	1	3	65	10	80
Kandahar zone	1	1	3	57	10	72
Herat zone	0	0	3	28	5	36
Total	4	4	20	232	38	298

1970, 3 541 643 vaccinations were performed and work was completed in 10 provinces (Fig. 14.4). Activities extended to Herat, the 4th zone, in 1971 and 4 676 442 vaccinations were performed during the course of the year. By the end of 1971, campaigns had been carried out in all but 4 provinces, and by June 1972, the first round of vaccination had been completed. In all, 10.5 million people had been vaccinated by a staff which at its maximum numbered only 298 persons (Table 14.5). The population of Afghanistan in 1972 was estimated by the government to be 17 million but, in the absence of a census, the actual number was unknown. The data of the smallpox eradication programme suggested that a population estimate of no more than 12–15 million persons would be more realistic.

On completion of the first round of vaccination, it was decided to undertake a second round, but to vaccinate only those under 15 years of age. The objective of this round was not so much to improve the immune status of the population as to ensure the continued mobility of the vaccination teams, who could both search for cases and detect the presence of variolators in the course of their work. The second round of vaccination was completed in 18 months, during which 5.4 million persons were vaccinated (see Table 14.4). The shorter time required reflected, in part, more efficient programme operations; of greater significance was the fact that village leaders were far more helpful and the villagers more receptive. After the second round of vaccination had been completed, it was decided to perform yet a third round, again to ensure a continuing search for cases and the detection of variolators. During the third round, only children under 5 years of age were vaccinated. This phase of vaccination was completed in just over a year, during which 1 621 774 individuals were vaccinated. Cooperation had progressed to such an extent in some areas that villagers assembled young children at collecting points, thus obviating the need for vaccinators to visit each house.

The nomadic and semi-nomadic Kuchis, who were estimated to number more than 2 million, presented a special problem. Entire families wintered in lowland pastures in southern Afghanistan and Pakistan, and, with their herds, moved to upland pastures in the spring. On the way, they travelled in large bands along comparatively well established routes, but once settled, they scattered widely, often in virtually inaccessible areas. Although, when settled, they readily accepted vaccination, they resisted it while travelling, fearing reactions to the vaccine. Many were vaccinated during the course of the systematic campaign but, as shown in a survey of Kuchis in Helmand Province in 1971, vaccinial immunity differed greatly from one group to another (Table 14.6). To ensure more complete coverage, a special summer programme was conducted during 1973 in Ghor and Bamian Provinces, in which the largest proportion was settled.

At the conclusion of the second round of systematic vaccination in 1973, the overall levels of vaccinial immunity in Afghanistan were assessed during a special programme. The levels of protection were among the highest found in any country (Table 14.7).

Table 14.6. Helmand Province: vaccination scar survey of Kuchi nomads, by age group, October 1971

Group	Proportion not protected			
	0–4 years		5–14 years	
	Number	%	Number	%
1	258	10	329	3
2	487	62	646	54
3	296	40	445	20

Table 14.7. Afghanistan: results of assessment for vaccination/variolation scars in 20 provinces, 1973

Zone/province	Number assessed	Proportion with scars (%)
KABUL		
Bamian	16 757	96
Ghazni	37 581	95
Kabul	75 178	96
Kapisa	23 291	97
Kunar	19 926	98
Laghman	18 082	96
Logar	11 137	95
Nangarhar	9 926	93
Paktia	56 466	97
KANDAHAR		
Chakansoor	6 017	97
Farah	5 039	93
Helmand	16 701	95
Kandahar	32 665	91
Oruzgan	16 705	92
Zabul	6 042	98
KUNDUZ		
Baghlan	26 776	93
Kunduz	27 448	93
Samangan	15 844	97
Takhar	34 834	97
HERAT		
Farlab	29 505	98

A Smallpox Surveillance Team

The investigation of a rumoured outbreak in November 1970 in the mountainous province of Oruzgan illustrates the pride and dedication that the teams developed. A team was sent on horseback to elicit information about the outbreak. On its way up a mountain, it encountered metre-deep snow and was forced to turn back. The team then approached the area by another route. Again, it encountered snow; the horses were abandoned and the team members continued on foot for 4 days to get to the villages. They stayed in the villages, moving from one to another to vaccinate. In all they spent 6 weeks vaccinating the inhabitants of villages in the middle of winter in the Oruzgan mountains. When it was possible to carry out a thorough search of the area in the spring, no cases of smallpox were found.

The Elimination of Smallpox: Epidemiological Patterns, 1969

Given the many problems and obstacles, the rapid development of a highly effective campaign of systematic vaccination was an extraordinary achievement. Programme staff, however, undertook at the same time an equally effective effort to improve reporting and to investigate and contain outbreaks. They decided that from September 1969, every reported case of smallpox would be investigated by a zonal containment team, usually accompanied by senior national and WHO staff. The Afghan programme was one of the very few in which both mass vaccination and surveillance–containment measures were simultaneously and successfully conducted.

To improve reporting, provincial medical offices were directed by the Minister of Health to report any suspected case by telephone or telegraph either to the national smallpox eradication office in Kabul or to the zone office. At the same time, the President of the Malaria Institute directed all malaria workers to report cases of smallpox. Meanwhile, programme staff began regular visits to each hospital, health centre and clinic to explain the programme and to ask that every suspected case or rumoured outbreak of smallpox should be reported promptly. Because only 69 out of 326 subdistricts had a health unit and because the malaria programme was not operational throughout the country as a whole, and not notably effective, additional measures were required. Zonal surveillance teams began systematic visits to the subdistrict civil authorities, the *maliks* and *arbabs*, to solicit their help and to visit the few existing schools. Each report of a case was investigated promptly by a surveillance team. The promptness of response provided tangible evidence to those reporting that the programme personnel were genuinely interested in receiving reports, and this gradually became widely known. Indeed, some villages which sought vaccination sent false reports, knowing that the report of a case would quickly bring a surveillance team to the village.

During the last 4 months of 1969, 22 reports of smallpox were received, of which 20 were verified to be outbreaks. In all, 79 cases were reported but the surveillance teams found an additional 171 cases during investigation (Table 14.8). In the course of 1970,

Table 14.8 Afghanistan: number of reported cases of smallpox and number of additional cases discovered by programme staff, 1969–1973

Year	Number of cases reported officially	Number of additional cases found by programme staff	Total
1969	79	171	250
1970	191	853	1 044
1971	192	544	736
1972	90	146	236
1973	10	15	25

Table 14.9. Afghanistan: source of reporting of outbreaks, 1969–1973

Source	1969	1970	1971	1972	1973
Provincial medical officers, hospitals, health centres and malaria agents	20	51	48	24	0
Local leaders	0	11	13	7	1
Programme staff	0	21	46	13	2
Total outbreaks	20	83	107	44	3

Definition of a Case of Smallpox among Variolated Persons

All persons who had been successfully variolated should properly have been recorded as cases of smallpox since they had been infected with variola virus. If all such individuals had been counted as cases, the recorded incidence in Afghanistan would have been high indeed, because in some outbreaks variolators performed upwards of 100 inoculations. To decide whether a person had been successfully variolated, however, was not a simple matter. The primitive technique of variolation often produced serious bacterial infections and it was impossible to tell whether or not variola virus had grown in the skin. For Afghanistan, and similarly for Ethiopia (see Chapter 21), it was agreed by WHO and the national authorities to record as cases only the variolated individuals who exhibited smallpox lesions on other parts of the body as well as at the site of variolation. It was recognized that some who were succesfully variolated would have a lesion only at the site of variolation and thus there would be an underenumeration of cases. However, because the probability of smallpox transmission was correlated with the extent of rash, such individuals were much less likely to transmit infection and therefore less important epidemiologically.

with reports being received from many additional sources (Table 14.9), the number increased to 1044 cases in 83 outbreaks. This was the highest total of cases recorded in Afghanistan since 1955. Cases were recorded in 21 of the 28 provinces (Table 14.10) and, as was the case in other countries, the apparent epidemic of smallpox (Fig. 14.5) alarmed the national authorities and fostered substantially greater support for the programme.

Table 14.10. Afghanistan: reported number of cases of smallpox, by zone and province, 1963–1973

Zone/province	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973
KABUL											
Bamian	21	0	2	5	0	0	0	24	50	0	0
Ghazni	0	0	0	2	2	5	0	37	3	37	13
Kabul	21	30	26	37	49	40	33	156	79	4	0
Kapisa	0	0	0	1	16	5	0	55	3	0	0
Kunar	0	0	0	0	15	18	3	9	12	0	0
Laghman	0	0	0	0	0	0	0	31	14	0	0
Logar	0	0	0	0	2	16	11	25	7	1	0
Nangarhar	31	0	0	11	0	1	88	68	30	54	0
Paktia	5	1	0	0	45	22	5	21	22	13	0
Parwan	52	2	5	6	1	16	9	0	0	0	0
Wardak	0	0	0	0	0	0	0	16	40	0	0
KANDAHAR											
Chakansoor	0	0	0	0	3	3	0	0	0	0	0
Farah	41	13	2	0	116	176	0	0	0	0	0
Helmand	183	9	14	2	3	5	9	0	0	2	0
Kandahar	18	49	11	0	19	19	0	3	1	13	11
Oruzgan	0	5	1	0	9	8	0	0	135	28	0
Zabul	0	0	0	0	3	4	1	30	6	65	1
KUNDUZ											
Badakshan	14	2	1	0	0	0	5	53	0	0	0
Baghlan	27	6	0	0	7	45	31	176	10	1	0
Balkh	121	17	4	0	4	60	0	7	142	0	0
Jawzjan	0	14	0	0	6	2	0	16	35	0	0
Kunduz	0	0	0	0	14	281	43	1	42	18	0
Samangan	0	0	0	0	4	0	0	0	0	0	0
Takhar	12	0	0	0	6	13	0	28	0	0	0
HERAT											
Badghis	0	0	0	0	10	0	11	0	9	0	0
Farlab	5	6	0	0	0	0	0	277	53	0	0
Ghor	0	21	0	0	0	0	1	1	33	0	0
Herat	26	3	4	2	0	0	0	10	10	0	0
Total	577	178	72[a]	66	334	739	250	1044	736	236	25

[a] Including 2 cases of unknown provenance.

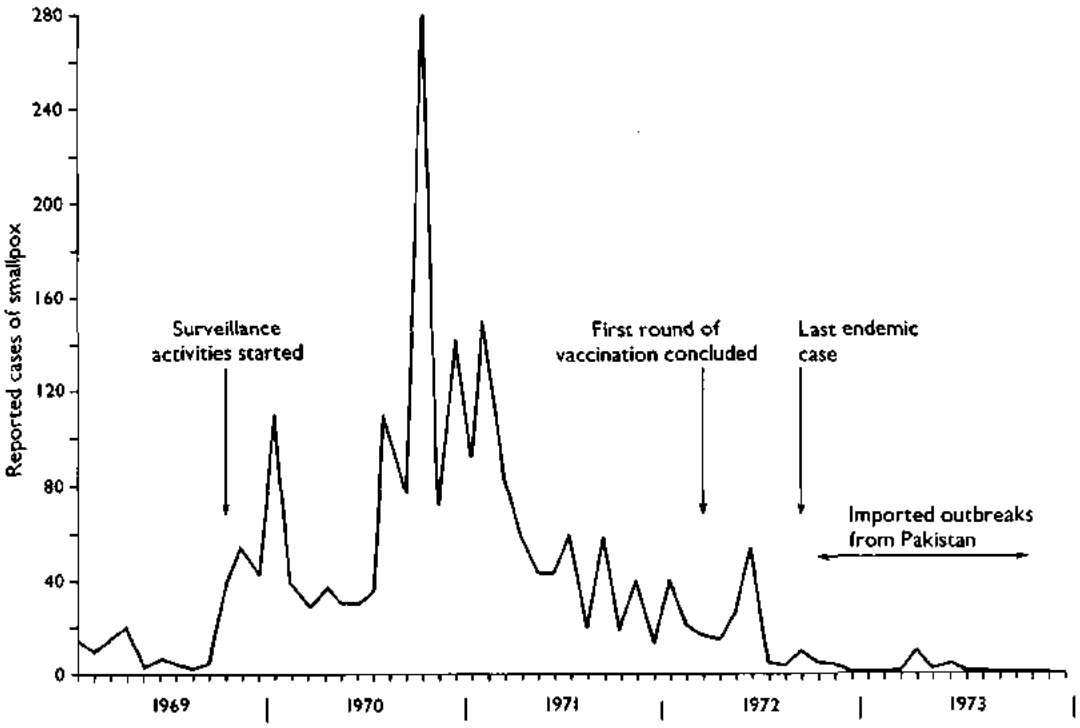


Fig. 14.5. Afghanistan: number of reported cases of smallpox, by month, 1969–1973.

Special concern was caused in 1970 by the increasing number of cases in the city of Kabul, and a number of outbreaks in other provinces which were traced to this source. In all, 156 cases (15% of all cases in Afghanistan) were reported from Kabul, most of which occurred in the congested poorer quarters of the city in which visitors from rural areas often stayed. Originally, vaccination in Kabul had not been planned since extensive vaccination campaigns had repeatedly been conducted there between 1962 and 1968. Because of the outbreaks, however, a special campaign was carried out during the winter months of 1970–1971. As in many other cities, the infectious diseases hospital itself proved to be a problem, 5 of the outbreaks resulting from the spread of smallpox within the hospital. One of the people infected was a Danish student, admitted because of suspected typhoid fever, who developed smallpox after returning to Copenhagen (see Chapter 23). This problem of hospital infection was eventually solved when smallpox eradication staff were assigned to the hospital to ensure the isolation of patients and the vaccination of all people admitted, for whatever reason. With these measures, Kabul and its infectious diseases hospital ceased to be a problem.

The number of outbreaks increased from 83 in 1970 to 107 in 1971, but only 736 cases were found on investigation, substantially fewer than the 1044 cases recorded in 1970.

In 1972, outbreaks were reported in only 11 provinces and the numbers of cases and outbreaks diminished rapidly. Between January and June, 10 provinces recorded 196 cases in 39 outbreaks. After June, smallpox was detected only in the southern provinces of Oruzgan, Kandahar and Zabul, the last indigenous cases occurring in Oruzgan in September, just 36 months after the surveillance–containment programme began. Later in the year, 1 outbreak occurred in Zabul and 2 in Kandahar whose sources of infection were, respectively, the towns of Pishin and Quetta, both in Pakistan.

The Final Outbreaks

Between October 1972 and April 1973, no evidence of endemic smallpox was found despite active search and the investigation of many rumours. However, 3 more outbreaks were yet to be discovered: 2 in April and 1 in June. The following brief descriptions of these outbreaks and how they were dis-

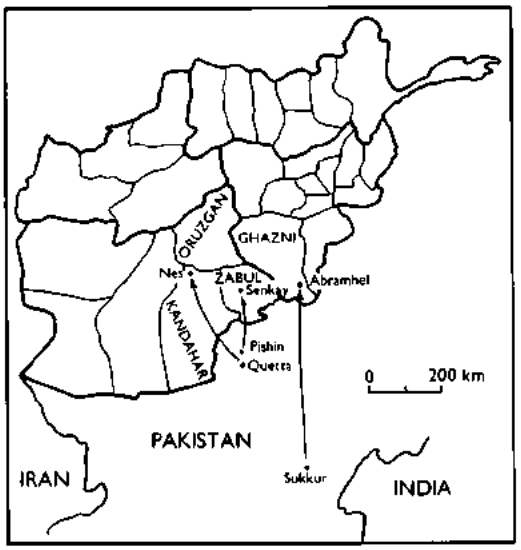


Fig. 14.6. Afghanistan: sources of infection and location of outbreaks, 1973.

covered, investigated and contained illustrate some of the challenges experienced by the Afghan staff.

Ghazni Province, Abramhel village

On 10 April 1973, a mobile vaccination team heard rumours from villagers of suspected cases in Wor Subdistrict, 85 kilometres away. The team leader and his supervisor went to the area the following day and in the village of Abramhel, 5 kilometres from a barely motorable road, found 3 active cases and 3 close contacts with fever, and learned of a person who had died of the infection. The village, consisting of 9 households and 56 persons, was one of a number of small, widely scattered villages situated on barren mountain slopes rising above an arid plain. A search of this and 12 neighbouring villages began immediately along with containment vaccination. In all, 2411 persons were vaccinated. Systematic vaccination had been conducted throughout the area 3 years earlier but this group of villages had been missed. The first case was that of a 23-year-old man who had travelled some 600 kilometres to the town of Sukkur in Pakistan in search of work (Fig. 14.6). He arrived back in his village after more than a year's absence, became ill with smallpox and died. In all, 13 cases eventually occurred, 2 of whom had old variolation scars and 7 of whom were vaccinated during the incubation period. Three of these persons died.

Zabul Province, Senkay Woleswali (*district*)

Fearing that Kuchi nomads might reintroduce smallpox during their spring migration from Pakistan, smallpox eradication teams in 1973 endeavoured to intercept groups of Kuchis in order to detect cases and vaccinate the others. On 29 April, a surveillance team found a 10-year-old child with smallpox among a group which was travelling from Pishin in Pakistan to its summer home in the mountainous province of Oruzgan. Only 5 of 140 persons in the group had not been vaccinated; the patient was one of the unvaccinated. The boy and his mother were isolated in the zone office and 2 vaccinators were assigned to travel with the Kuchis to detect any further cases that occurred. The Kuchis, who were smuggling cloth, feared that they might be reported and left silently, leaving the mother and child and 2 sleeping vaccinators. Angered by this, the mother revealed the intended route and destination of the band, and a vaccination team again intercepted them to keep them under surveillance for 6 weeks. No further cases occurred.

Kandahar Province, Nes Subdistrict

As happened in several countries, the final outbreak was marked by delays and failures in reporting in what was then thought to be a reasonably effective system of notification and containment. On 3 July 1973, the zone office in Kandahar was informed that a number of deaths had occurred in a Kuchi nomad camp some 90 kilometres to the north. Five days had elapsed since the commandant of police at Nes had telephoned this information to police headquarters in Kandahar. The provincial medical officer was notified the same day and he immediately sent a laboratory technician to investigate. The technician returned on 30 June to confirm that the outbreak was smallpox. Instead of directly informing the zone office, a few blocks away, the provincial medical officer wrote a letter to the office on 2 July which was received late the next day. On 4 July, the zone team went to Nes, where they found a Kuchi camp of 45 persons living in 7 tents. In all, 11 cases with 5 deaths had occurred. Surprisingly, a local malaria surveillance agent had visited the camp several days earlier, vaccinated a few people and departed without notifying anyone. Meanwhile, on 2 July, a variolator who lived in Nes had visited the camp, gathered scabs from one of the patients, variolated 10

persons and departed for another province. The team conducted an immediate search and vaccinated the population of the subdistrict, performing some 2300 vaccinations in all. Nine of the 11 cases were among adults. Systematic vaccination had been completed in the subdistrict only 3 months before, but at the time of the team's visit, only the children and a few women had been in camp, the men having gone far ahead to prepare the next campsite. The first case in the outbreak had been that of a 35-year-old man who had accompanied his uncle to a hospital in Quetta, Pakistan, and had developed smallpox after his return. A cable to Quetta confirmed that at the time of his visit, cases were present in the hospital. Thus, the last known outbreak in Afghanistan was traced to infection probably acquired in a hospital; the report of the outbreak and its containment were delayed by a full 5 days because of poor communication; a health worker who should have reported the cases failed to do so; the men in the camp who should have been vaccinated only 3 months earlier were missed because they had travelled to another area; and a variolator was given the opportunity to acquire scabs. Despite extensive search the variolator was never found nor was another case of smallpox detected in Afghanistan.

Conclusion of the Programme

The last outbreaks in Afghanistan were cause for celebration, but with smallpox still endemic in Pakistan and with the spectre of its possible recurrence through the practice of variolation, programme staff could not relax their efforts. The tens of thousands of nomads who began their annual trek northwards out of Pakistan in late February and March were of particular concern. In 1973, the number of surveillance teams in southern Afghanistan was increased and a special programme was begun to intercept nomads during their travels. During this period, different surveillance teams succeeded in intercepting some nomadic groups so often that the leaders of the groups protested against the harassment. To deal with the problem, it was decided to issue a special certificate to the leader after all members of a group had been examined, provided that they all accepted vaccination. When subsequently intercepted by another surveillance team, the group leader simply presented the certificate, assuring the nomads of the right of passage without further examination. Happily, the procedure was well accepted.

Meanwhile, the systematic vaccination campaign was continued, primarily to sustain a continuing search for cases but also to keep the number of susceptible persons as low as possible and so diminish the chance of variolation being revived. In fact, as late as 1976, evidence of attempted variolation was found, but no successful variolations are known to have occurred following the last outbreak in 1973.

Finally, after the interruption of smallpox transmission in Pakistan in October 1974, a reward of 1000 afghanis (US$18) was offered to anyone reporting a case. The number of rumours and reports of suspected cases increased dramatically but, on investigation, none proved to be smallpox.

Epidemiological Data

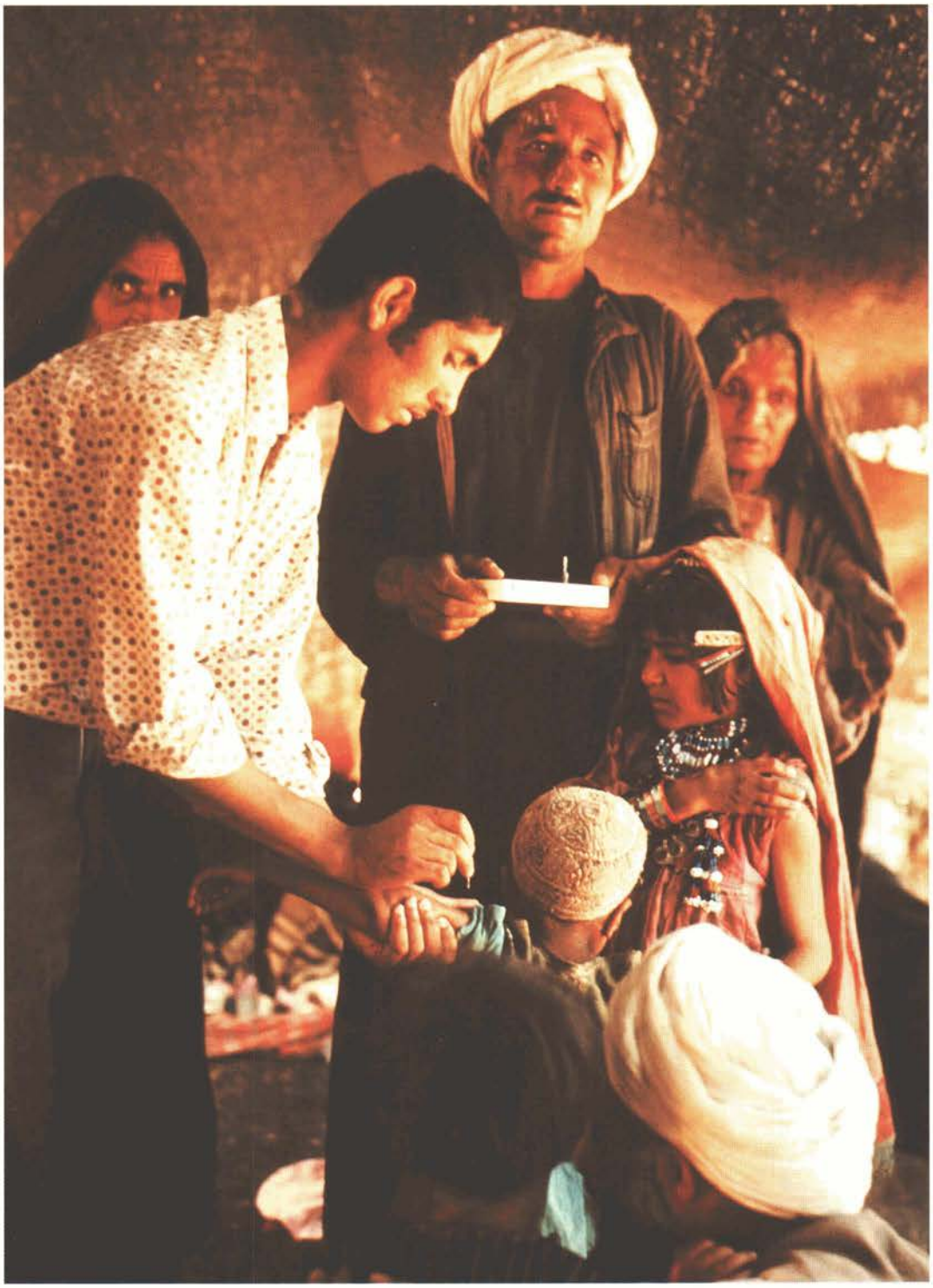
Data on age and vaccination status are available for 2258 of the 2291 cases that occurred between 1969 and 1973 (Table 14.11). Of the total, 360 cases (16%) were among persons infected through variolation. Only 83 (4%) occurred among those who had been vaccinated before exposure.

Because of the isolation of so many villages and areas in Afghanistan and the difficulty of movement from place to place, it was expected that a much larger proportion of cases would be found among adults, but in fact the proportion was not much greater than in

Table 14.11. Afghanistan: reported number of cases of and deaths from smallpox, by age group, 1969–1973[a]

Age group (years)	Cases		Number naturally infected		Number variolated	Number of deaths
	Number	%	Vaccinated	Unvaccinated		
<1	121	5	0	90	31	26
1–4	821	36	8	668	145	127
5–14	1031	47	36	840	155	106
⩾15	285	12	39	217	29	54
Total	2258	100	83	1815	360	313

[a] Excluding 33 cases for which data are not available.



WHO / P. ALMASY

Plate 14.4. An Afghan worker vaccinates members of a nomad family in their tent.

WHO / P. ALMASY

WHO / BABY

Plate 14.5. **A:** A nomad encampment in the vast, sparsely settled central mountain plateau of the Hindu Kush, Afghanistan. **B:** A Pakistani woman waves the traditional *neem* leaves over a sick child. Throughout much of the Indian subcontinent, the leaves of the *neem* tree were believed to have special healing powers over smallpox.

Indonesia (11%), with its dense population, and far smaller than in Pakistan (37%). The paucity of susceptible adults reflects the extent of previous smallpox and variolation.

The overall case-fatality rate of 13.8% (313 deaths among 2258 cases) understates the severity of natural infection, including, as it does, 360 cases infected by variolation, among which the case-fatality rate was often 2-3%. Discounting variolation, the case-fatality rate was about 16%, a figure approximating to that found in the Indian subcontinent.

The source of infection of the 237 outbreaks that occurred from 1970 to 1973 is shown in Table 14.12. Of the 201 outbreaks for which a source could be identified, 45 (22%) represented importations from Pakistan and 47 (23%) resulted from variolation. During this 4-year period, the teams investigated a further 345 outbreaks reported to be smallpox but which, on investigation, proved to be chickenpox (202), measles (51) and other skin infections (43). The remainder were rumours without apparent foundation.

Table 14.12. Afghanistan: sources of infection of outbreaks, 1970–1973

Source	1970	1971	1972	1973	Total
Pakistan	11	13	18	3	45
Variolation	23	21	3	0	47
Other sources in Afghanistan:					
Nomads	8	4	5	0	17
Hospitals	5	2	0	0	7
Other	16	55	14	0	85
Unknown	20	12	4	0	36
Total	83	107	44	3	237

Outbreaks which resulted from importations, with one exception (in Badakshan Province), occurred in areas south of the Hindu Kush mountain range in provinces near or on the border with Pakistan. Similarly, outbreaks traced to the nomads (except those in Badghis Province) who migrated from Pakistan to Afghanistan were in these same areas (Fig. 14.7).

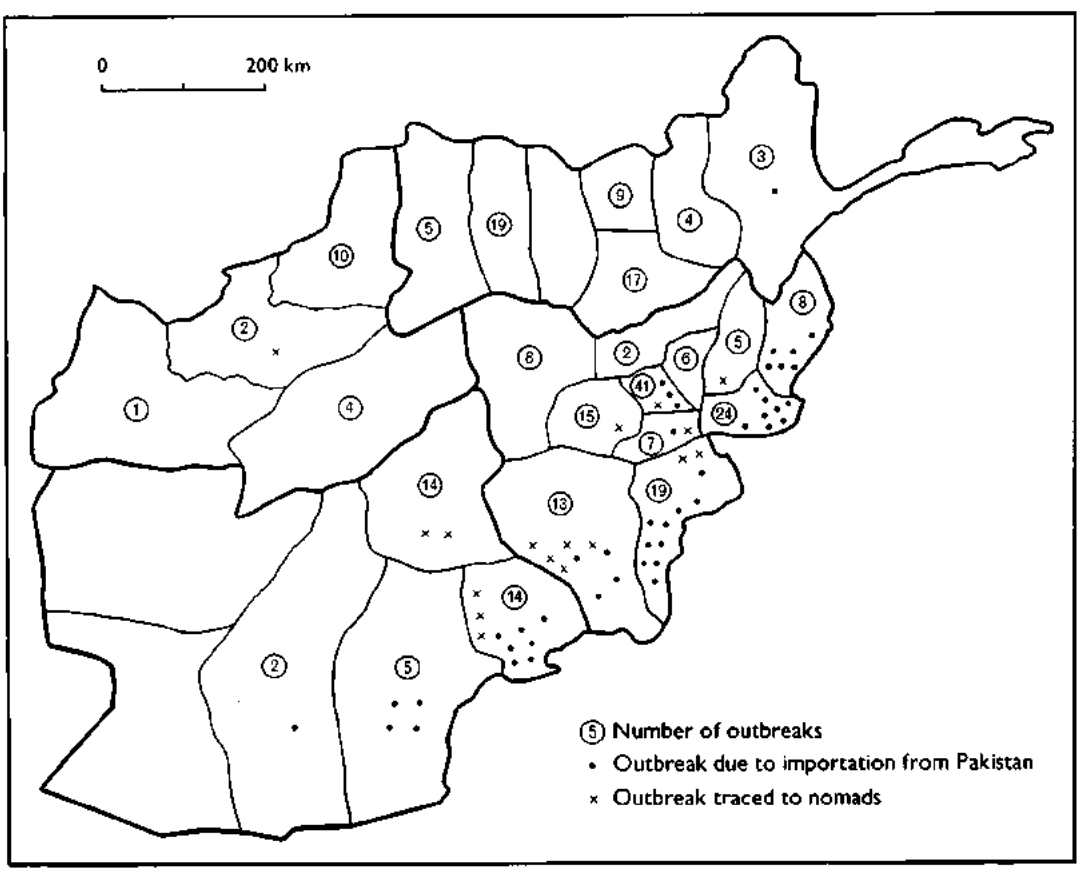


Fig. 14.7. Afghanistan: number of outbreaks by province and location of those caused by importations from Pakistan and those among nomads, 1969–1973.

Delays in the detection of outbreaks (Table 14.13) were a problem throughout the programme. The mean interval was just under 4 weeks, the delays being as great in 1972 as they were in 1969–1970. After the outbreaks had been found, however, further transmission did not continue for long. In only 6 out of 224 outbreaks did new cases occur more than 2 weeks after containment had begun, even though many of the outbreaks were on a large scale (Table 14.14).

The Problem of Variolation

Variolation had been thought to be a major, perhaps insoluble, problem. The practice was most widespread in the more remote mountainous villages and among the nomadic Kuchis, its extent being in inverse relation to the people's ease of access to vaccination. Among the adults in some areas, upwards of 50% bore the scars of variolation. For some, variolation was the only available protection against naturally occurring smallpox and many continued to pay to have variolation performed, even when free vaccination became available. Variolation was a familiar procedure to them and they regarded it as providing permanent immunity.

Priority was given to the identification of variolators: to characterize them, learn about their practices, obtain variolation material from them and persuade them to abandon the practice or to accept vaccine for use instead of variola virus. This was difficult, however, because they feared punishment if they were discovered. Between 1969 and 1973, 61 variolators were contacted and persuaded to abandon the practice. Later, in 1976, a special search for variolators revealed 36 others. The location of the variolators by province is shown in Fig. 14.8. Undoubtedly the numbers found represent only a small fraction of the total.

The variolators performed variolation only on the request of a village or a family, and usually for a fee. Many were farmers and some were religious leaders; other practitioners who were identified included a tailor and 4 women. In almost all cases, the variolator's father and grandfather had also been variolators and usually only the eldest son was engaged in the practice. Scabs—rarely pustular material—were collected from a recovering patient, preference being given to patients with many lesions who could therefore provide a greater amount of material. None of those interviewed said that they selectively sought to obtain scabs from less severe cases on the assumption that virus from such cases might result in less severe reactions. The scabs were usually kept either as such or in a powdered form. Sometimes, a liquid (e.g., honey or spices in water) was added either soon after the scabs had been obtained or immediately before inoculation. Because variola virus is exceptionally stable when dried, especially if kept in a cool place, efforts were made to learn from the variolators how long they believed they could satisfactorily store the virus. Most of them stated that it was necessary to obtain new material each year. A few observed that material could be retained for as long as 2 years, but they noted that such material was not reliable and often did not induce the desired infection.

Table 14.13. Afghanistan: number of outbreaks according to interval between first case and notification and between beginning of containment and last case, 1970–1973[a]

Number of days' interval	Number of outbreaks according to:	
	Interval between first case and notification	Interval between beginning of containment and last case
0–7	15	209
8–14	38	9
15–21	32	2
22–28	45	3
29–35	34	1
36–42	18	–
43–56	26	–
>56	16	–
Total	224	224

[a] Data available for 224 out of 237 outbreaks.

Table 14.14. Afghanistan: number of cases of smallpox per outbreak, 1969–1973[a]

Number of cases	Outbreaks	
	Number	%
1	60	24
2–5	82	32
6–10	57	23
11–50	49	19
>50	6	2
Total	254	

[a] Data available for 254 out of 257 outbreaks.

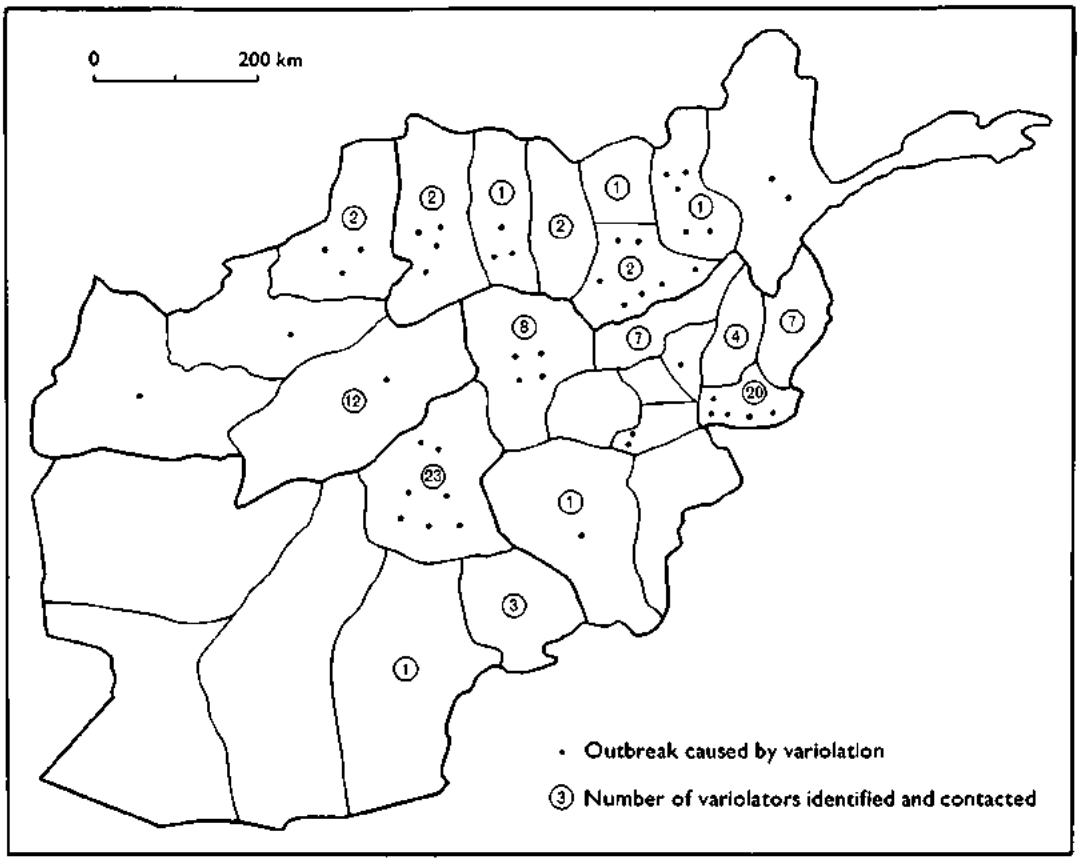


Fig. 14.8. Afghanistan: location of variolators who were identified and of outbreaks caused by variolation.

The variolators kept the scabs in all manner of jars and boxes, usually in their houses. A particularly interesting case was that of a variolator who kept the material in a horn, stored in a cave at a high altitude, quite far from his home. Although storage in a cold environment such as this should have served well to preserve the virus, the variolator reported that the material he collected was not very effective if more than a year old.

Six specimens were obtained and tested in WHO reference laboratories. Variola virus was isolated from 4 of them, of which 2 had titres that were presumably high enough to induce infection if inoculated (Table 14.15). The 4 specimens from which virus was isolated were collected between March 1969 and April 1970. One specimen collected in April 1976 consisted of scabs said to have been obtained in Pakistan in October 1974. In this specimen, virions were seen by electron microscopy but the virus did not grow on egg membrane.

Variolators were usually known to villagers throughout a subdistrict or district and were summoned only when smallpox began to occur in the area. However, some variolators travelled considerable distances, offering their services to the headman of each village visited. Sometimes, all the susceptible individuals in an entire village were systematically vaccinated, ensuring that none would remain to be exposed to natural infection acquired from those who had been variolated. This was the exception rather than the rule, however.

The usual method of variolation was to suspend the powdered scab material in a paste and to inoculate it either on the dorsum of the forearm or on the wrist, adjacent to the extensor tendon of the thumb (referred to by physicians as "the anatomical snuffbox"). Some did this by superficial linear scratch using a knife and some by multiple puncture using a small bundle of needles. A bandage was then placed over the area. Fever began on

Table 14.15. Afghanistan: results of laboratory testing of specimens collected from variolators

Number	Type of specimen	Date of collection	Age of specimen	Technique			Titre (pock-forming units/ml)[a]
				Electron microscopy	Gel precipitation	Variola virus isolation	
1	Fluids	March 1969	?	*b*	*b*	+	2 500
2	Scabs	May 1969	9 months	*b*	*b*	+	10 000
3	Scabs	September 1969	4 months	*b*	*b*	+	30
4	Scabs	April 1970	?	*b*	*b*	+	14
5	Scabs	January 1972	?	–	–	–	–
6	Scabs	April 1976	18 months	+	+	–	–

[a] Titre of vaccinia virus necessary to obtain successful vaccinations in 50% of those vaccinated—about 300 pock-forming units per ml.
[b] Not performed.

about the 4th or 5th day and a lesion appeared on the 7th day. Many of those inoculated developed lesions elsewhere on the body and, although the variolators who were interviewed usually denied that any of their patients had more than 100–200 lesions, surveillance teams found some with more extensive rashes and learned of others who had died.

Between 1970 and 1972, 47 out of 237 outbreaks were caused by variolation. These occurred primarily in provinces lying north of the Hindu Kush range and in the central mountainous provinces of Bamian and Oruzgan (Fig. 14.8). As is shown in Table 14.16, 714 cases occurred in outbreaks which had been initiated by variolation—i. e., more than one-third of all cases in Afghanistan during this 3-year period.

Certainly, variolation was a problem, but considering the large number of traditional variolators, it was less serious than had been

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Plate 14.6. A variolator demonstrates the traditional way of binding the site of inoculation after variolation. The picture was taken in Afghanistan in 1970.

Table 14.16. Afghanistan: number of cases of smallpox due to variolation, 1970–1972

	1970	1971	1972
Number of outbreaks initiated by variolators	23	21	3
Number of cases due to variolation	120	200	16
Number of additional persons infected in the outbreak	213	158	7
Total number of cases directly or indirectly due to variolation	333	358	23
Total number of cases during the year	1 044	736	236
Proportion of cases related to variolation	32%	49%	10%

expected. Because vaccination was known to most of the population—though it was not always easily available—variolation had already begun to disappear by the time the programme in Afghanistan commenced. The efforts of the surveillance teams to contact all village and subdistrict leaders and to explain to them the adverse consequences of variolation undoubtedly helped to diminish the practice. The immediate response of the surveillance teams to any reports of smallpox cases was also important: vaccination was made widely and freely available before the variolators were able to initiate their activities.

PAKISTAN

Pakistan and its smallpox eradication programme presented a contrast to the situation in Afghanistan. Most of West Pakistan's 60.5 million people (1967) lived in the vast Indus river plain and in the Himalayan foothills, where population density was high. The government structure throughout this area was comparatively sophisticated, health services were much more extensive and health personnel were far more numerous than in Afghanistan. A network of roads, as well as train and air connections, and postal and telegraph services facilitated communication. Throughout this area, a programme of smallpox vaccination had been in operation for nearly 100 years; vaccinial immunity was high and variolation was all but unknown. Some remote, sparsely populated areas, however, presented problems almost as formidable as those in Afghanistan. In the northern mountainous areas of Gilgit and Azad Kashmir, in the mountainous districts bordering on Afghanistan and in the vast western deserts of the Baluchistan plateau, government and health services were less well developed, health personnel were few, vaccination had been less extensively practised and a few persons were still being variolated. The inhabitants of such areas, however, constituted no more than 10–15% of the country's total population.

In 1967, Pakistan consisted of the provinces of West Pakistan and East Pakistan, separated by the breadth of India and, each essentially autonomous so far as health programmes were concerned. In July 1970, the government decided to divide West Pakistan into 4 provinces and 2 federal regions. Health continued to be a provincial responsibility, the Federal Ministry of Health retaining authority only for health policy, the direction of medical research, standards of medical education and relationships with international organizations. A single smallpox eradication programme in West Pakistan thus became 4 separate and autonomous provincial programmes and 2 federal regional programmes which differed greatly in their methods of operation, rate of progress, and degree of political commitment to eradication. What little coordination existed between the programmes was achieved primarily by the WHO advisers. In December 1971, East Pakistan became the independent country of Bangladesh, whose programme is described in Chapter 16. The present chapter deals only with West Pakistan, designated, since 1971, as Pakistan.

Because of the availability of resources and the more sophisticated government and health structure, the eradication of smallpox appeared to be more feasible in Pakistan than in Afghanistan. Surprisingly, transmission was not interrupted until October 1974, 2 years later than in Afghanistan. Even when the last cases were being detected, the case notification procedure and surveillance system were still so inadequate that many months were to elapse before either national or WHO staff were persuaded that eradication had been achieved. Adherence to traditional mass vaccination, erratic political commitment and poor management were to characterize the programme throughout most of its course.

Smallpox before 1967

As in Afghanistan, only variola major, the severe form of smallpox, is known to have

occurred in Pakistan; and in past centuries, variolation had been widely practised. Smallpox control through vaccination began during the colonial period, before British India became the independent countries of Pakistan and India, and was widely practised throughout the more populous areas until the late 19th century. In the former province of Punjab, which constitutes a major part of Pakistan, a large-scale programme of vaccination began in 1875 under a General Superintendent of Vaccination, who employed 29 supervisors and 121 vaccinators. A Vaccination Act was passed in 1880, and in 1888 local government bodies were created which were responsible for vaccination programmes in their own areas. Indeed, throughout the 1970s, vaccination by "local body vaccinators" (personnel paid by local government authorities) continued in most parts of Pakistan. Liquid vaccine produced at the Punjab Vaccine Institute in Lahore was used. The extent of vaccination is illustrated by data from the former Punjab Province for the period 1933–1938. Each year, 3.1–5.8 million vaccinations were recorded in the province, whose population was only 24.8 million (1935) (Table 14.17). Nevertheless, the number of notified cases of smallpox remained high and major epidemics recurred every 4–6 years.

Table 14.17. Punjab Province of British India: number of vaccinations performed and number of cases of and deaths from smallpox, 1933–1938

Year	Number of vaccinations	Number of cases	Number of deaths
1933	3 206 356	22 571	11 626
1934	3 113 487	3 595	1 962
1935	4 485 935	3 592	1 822
1936	3 549 081	6 158	2 613
1937	5 774 130	10 040	3 991
1938	4 629 327	12 307	5 455

Table 14.18. West Pakistan: number of reported vaccinations as a percentage of population and number of reported cases of smallpox, 1959–1968

Year	Population (thousands)[a]	Vaccinations		Number of cases
		Number (thousands)	As % of population	
1959	48 912	8 833	18.1	3 373
1960	50 093	6 777	13.5	815
1961	51 442	10 265	20.0	2 408
1962	52 827	15 486	29.3	3 484
1963	54 250	14 439	26.6	1 929
1964	55 711	12 679	22.8	935
1965	57 211	14 878	26.0	1 285
1966	58 817	18 759	31.9	2 936
1967	60 469	22 681	37.5	6 084
1968	62 166	13 946	22.4	1 836

[a] Population estimates from United Nations (1985).

Although the vaccination campaign undoubtedly had an impact on the incidence of smallpox, the effect was not impressive in comparison, for example, with that of the campaign in Indonesia, in which smallpox was eliminated during the same period. This was probably due to the fact that the vaccine used in Punjab was the thermolabile liquid product rather than the dried, heat-stable variety employed in Indonesia.

Following independence, local body vaccinators continued to vaccinate using the liquid vaccine. In the period 1959–1968 the reported number of vaccinations performed each year represented a proportion of the population ranging from 14% to 38%; moreover, the number of primary vaccinations reported to have been performed was greater than the number of newborn infants. In view of the fact that, in 1968, there was 1 vaccinator for every 40 000 persons, the numbers of reported vaccinations are believable. None the less, smallpox continued to occur, with peaks in incidence every 4–6 years (Table 14.18). As later studies were to show, the number of reported cases was only a fraction of the total that actually occurred. However, the once widely prevalent practice of variolation ceased in all but a few remote, less populous mountainous and desert areas, where it continued to exist until the end of the programme.

Programme Strategy

Immediately after the decision of the Nineteenth World Health Assembly in 1966 to intensify the smallpox eradication programme, the Director of WHO's Regional Office for the Eastern Mediterranean, who fully supported the programme, had recruited the energetic Dr Ehsan Shafa, a veteran of Iran's successful smallpox eradication programme of the early 1960s, as the regional adviser on smallpox eradication. In March 1967, Dr Shafa first consulted government officials in Lahore to discuss the development of a programme. Separate schemes were drawn up for East and West Pakistan. The

Plate 14.7. After a vaccination session, Pakistani schoolchildren hold their sleeves away from their arms to allow the remaining vaccine lymph to dry off. This was the customary practice with liquid vaccine in most countries, although vaccinations were equally successful if the excess moisture was wiped off immediately. In many countries in which mass campaigns were conducted, only a small proportion of the children attended school but they were often vaccinated at 6-month intervals by vaccinators eager to fulfil the quotas set for them.

plan of operations was signed by WHO in August 1967 but not by the government until April 1968.

The procurement of supplies began in the hope that the programme might be launched by the end of 1968. A WHO adviser was assigned in September 1968 and supplies were delivered that autumn. However, the programme did not commence until June 1969. Five more years were to elapse before smallpox transmission was finally interrupted. A host of administrative problems hampered the programme from its inception, and during 1971, activities everywhere were curtailed because of the civil war. However serious these problems, the principal deterrent to progress was the protracted delay in taking cognizance of the findings of a group of investigators at the Pakistan Medical Research Centre in Lahore and of the strategy worked out by them.

The Lahore centre was supported by the government of Pakistan and the United States National Institutes of Health; it was one of four international centres for medical research and training in which United States and local scientists collaborated in medical research programmes. The investigators themselves decided which studies should be undertaken; those in the Pakistani centre decided to study the epidemiology of smallpox in West Pakistan. In May 1966, they began a 1-year study of smallpox in a rural district with a population of 1.2 million near Lahore and later undertook additional studies in urban Lahore and in other districts better to define the epidemiology of the disease (Ali & Heiner, 1971; WHO/SE/69.13, Heiner et al.; Heiner et al., 1971a,b; Mack et al., 1970, 1972a,b; Thomas et al., 1972). The studies, which are described in the next section, were the most comprehensive to be undertaken during the whole global eradication programme. The principal investigators (Dr Ashgar Ali, Dr Nusrat Fatima, Dr Gordon Heiner, Dr Muzaffar Khan, Dr Fred McCrumb, Dr Thomas Mack and Dr David Thomas) prepared a series of important papers which were distributed to WHO smallpox eradication programme staff throughout the world beginning in 1968; most of these papers were published in scientific journals between 1969 and 1972. The data argued persuasively for giving the highest priority in Pakistan to the detection and containment of outbreaks, especially during the season of lowest incidence, and to special vaccination campaigns in urban areas. The applicability of the strategy was soon supported by observations in western Africa, Brazil, Indonesia and East Pakistan, as programmes throughout the world gave increasing emphasis to surveillance and containment. Ironically, West Pakistan was among the last to commit itself fully to this strategy.

In most countries, but especially those in the Indian subcontinent, the belief that it was necessary to vaccinate every member of the population to achieve eradication was accepted doctrine. That the development of reporting and surveillance systems was at least equivalent in importance to mass vaccination was an alien concept. In West Pakistan, the principal WHO advisers up to 1971 were veterans of the successful eradication programme in Iran in the early 1960s. There, smallpox transmission had been interrupted through a large-scale vaccination campaign;

surveillance was an unknown quantity. However rational the surveillance–containment strategy might be, it was extensive vaccination to which they were committed and to which they devoted their principal energies.

Before describing the programme and its evolution in West Pakistan, it is of interest to review the findings of the group from the Pakistan Medical Research Centre, which document the status of smallpox and its epidemiology in West Pakistan at the time the programme began.

Studies of Smallpox in West Pakistan, 1966–1967

Investigators from the Pakistan Medical Research Centre first studied the occurrence and patterns of transmission of smallpox over a 1-year period, beginning in May 1966 in a single district. Their stated objective was to determine the best strategy to interrupt transmission (Mack et al., 1970, 1972a,b; Thomas et al., 1972). Sheikhupura District, an agrarian area of 2312 square kilometres and a population of 1.2 million, of which 85% lived in 1700 villages, was selected for study. Since 1946, the district had recorded about 50 smallpox cases per annum with occasional years during which several hundred cases were reported. During the 1-year period of study, cases were identified by the epidemiologists through the field investigation of reports to the district health officer and rumours received from civil servants and travellers and through routine inquiries in villages. Control measures, if conducted, were performed by the local health authorities.

During the year of study, 146 cases in 23 villages were officially reported to the district health officer. The investigators, however, discovered 1040 cases in 121 outbreaks and subsequently estimated, by sample survey, that an additional 40 outbreaks and approximately 180 cases had occurred that had not been detected. Thus, even in this district, which had a reasonably extensive health structure, little more than 10% of all cases were being reported. The true incidence was about 1 case per 1000 population, a figure far higher than that recorded in the most highly endemic countries during this period and an incidence substantially greater than was detected subsequently in any year in any district of West Pakistan.

Data regarding the age and outcome of illness were reported for 1034 of the patients. The age distribution and case-fatality rates were similar to those observed elsewhere in the Indian subcontinent: 29% of cases occurred among children under 5 years of age and a similar percentage (28%) among persons aged over 15 years (Table 14.19). In all, 16% died, but among infants (under 1 year) case-fatality rates reached more than 50%.

Despite the substantial number of cases, sample surveys of 15 villages showed a remarkably high proportion of persons who had previously been vaccinated. Among 6000 persons examined, 88% had either vaccination scars or the pockmarks of smallpox (Thomas et al., 1972). Three-quarters of the cases had occurred among the 12% who had not been vaccinated before exposure (Table 14.20). Among the unvaccinated household contacts of cases, 88% developed smallpox, compared with only 7% of people who had been vaccinated at some time.

Table 14.19. West Pakistan, Sheikhupura District: number of reported cases of and deaths from smallpox and case-fatality rates, by age group, 1966–1967[a]

Age group (years)	Cases		Number of deaths	Case-fatality rate (%)
	Number	%		
<1	68	7	38	56
1–4	232	22	32	14
5–14	445	43	46	10
⩾15	289	28	46	16
Total	1034	100	162	16

[a] Based on Mack et al. (1970).

Table 14.20. West Pakistan, Sheikhupura District: secondary attack rates in infected compounds[a]

	Number of contacts in compound	Number of cases among contacts	Secondary attack rate (%)
Not vaccinated before exposure	43	38	88
Vaccinated 0–10 days after exposure	16	12	75
Not vaccinated	27	26	96
Vaccinated before exposure	180	13	7
More than 10 years before	65	8	12
Within preceding 10 years	115	5	4
Previous smallpox	27	0	0
Total	250	51	20

[a] Based on Mack et al. (1972a).

Studies of smallpox transmission in 6 rural districts showed that vaccinated persons who experienced infection transmitted the disease to others only one-fourth as often as did unvaccinated persons with smallpox (Heiner et al., 1971b; see Chapter 4, Table 4.10).

In brief, smallpox transmission was sustained primarily by perhaps 150 000 persons of Sheikhupura District's 1.2 million residents. Pakistan's vaccination campaign had been more effective, at least in this district, than had been thought. A later study, done in Lahore Municipal Corporation, showed even higher levels of protection. In Lahore, 93% of all persons surveyed showed vaccination scars or the pockmarks of smallpox. Even among infants under 1 year of age 39% were protected, and among children aged 1–4 years 84% were protected (WHO/SE/69.13, Heiner et al.; Ali & Heiner, 1971).

The seasonal fluctuation in incidence was significant (Fig. 14.9), the peak occurring during the colder, drier months of November to the end of March. By September, at the end of the hot summer monsoon, smallpox had all but vanished (Thomas et al., 1972); in the first week of September 1966, only 1 village in the entire district was infected. However, even at the peak of the transmission season, not more than 50 of the 1700 villages in the district were infected at one time.

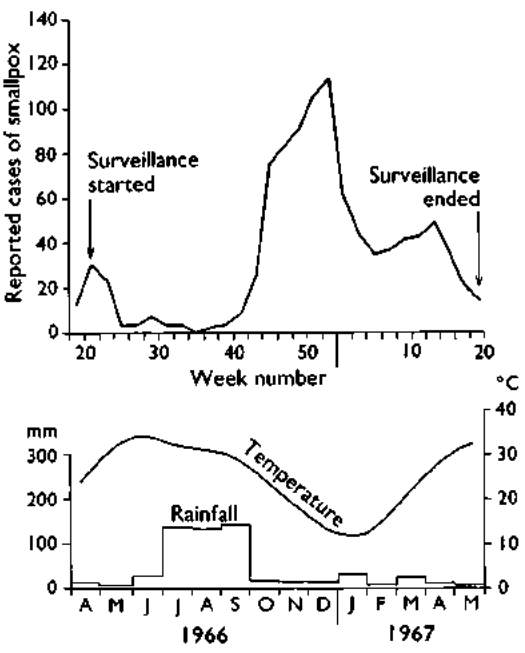

Fig. 14.9. Pakistan, Sheikhupura District: number of reported cases of smallpox in relation to meteorological data, by 2-week intervals, 1966 – 1967.

The outbreaks were often small and most terminated spontaneously. Smallpox was found to spread far less readily than measles or influenza, for example. Nearly one-third of the outbreaks consisted of single cases and in only half of the 121 outbreaks did new cases develop more than 4 weeks after the first case had occurred (Thomas et al., 1972). Even when transmission did occur, an average of only 2.4 new cases was recorded during each 2-week period. The larger outbreaks were of greater epidemiological importance. More than 50% of outbreaks with 5 cases or more were identified as sources of other outbreaks, compared with only 15% of outbreaks with fewer than 5 cases.

Contrary to what many supposed, smallpox was rarely transmitted at large public gatherings or transferred from place to place by nomads. Most infections were acquired as a result of contact with the patient in his own home (Thomas et al., 1972).

A further significant observation was the identification of large urban areas as important foci for spread. Of 74 outbreaks for which a specific source of infection could be determined, 42 (57%) could be traced directly or indirectly to cities, in which only 19% of the Punjabi population resided (Thomas et al., 1972).

The group of investigators pointed out that if Sheikhupura District and the Lahore Municipal Corporation were representative of other areas with regard to vaccinial immunity levels, a mass vaccination campaign had, to all intents and purposes, already been carried out. They recommended that instead of conducting another mass campaign, attention should be focused on the detection of cases and the containment of outbreaks, especially in urban areas. Such an approach would be especially effective during the summer, when only a few localities were infected. Because the disease spread slowly within and between villages, they believed that few resources would be required to cope with the outbreaks. Even if the reporting of cases was not improved, the effective containment of those that did come to notice should have a significant impact, since, as had been found, the larger outbreaks were reported more often and were most frequently responsible for spread to other localities. Because of the importance of cities in transmission, it was reasoned that urban areas should be given priority in mass vaccination campaigns, if such were to be conducted, and that emphasis should be placed on primary vaccination.

The observations in Sheikhupura District were subsequently found to be applicable throughout most of Pakistan. Not all areas had as high levels of vaccinial immunity as Sheikhupura, but everywhere successful immunization had been far more extensive than anyone had believed and the epidemiological pattern of spread of smallpox was similar. The recommendations of the group of investigators proved to be sound when they were eventually put into practice in Pakistan in 1972.

Beginning of the Mass Vaccination Campaign, 1968–1969

The plan of operations was signed in August 1967 by WHO and in April 1968 by the government, in Islamabad. Planning, procurement of supplies and recruitment of staff took longer than expected, but in June 1969 field operations finally began. West Pakistan, in 1969, was divided into 6 health regions, each comprising about 8 districts. Each district had a population of 1–2 million. The plan called for systematic mass vaccination campaigns in 2 regions each year. When the mass vaccination campaign was completed in a region, maintenance vaccination would be introduced to vaccinate neonates and migrants and to revaccinate the entire population every 3–4 years (Table 14.21).

The inhabitants of the two most populous health regions of Sargodha and Lahore, in which Sheikhupura District was located (Fig. 14.10), would be the first to be vaccinated. The campaign was to be directed by 2 provincial medical officers assisted by the WHO adviser and, at each health region office, by 2 medical officers, plus supporting clerical staff. At the health region level, a unit composed of 10 vaccinators and a superintendent of vaccination were to undertake surveillance activities and to control epidemics. The primary operational unit was the district, in which the campaign was to be directed by a full-time medical officer, a district superintendent of vaccination and teams of 10 vaccinators. A complement of 50 vaccinators for every million persons was considered necessary. This number was determined on the assumption that each vaccinator would perform an average of 100 vaccinations a day over 200 working days each year. Each operational group of 50 vaccinators would have a group leader and 5 assessors to check performance; vaccination was to be conducted village by village and house by house, the inhabitants of each locality to be vaccinated systematically by an operational unit of 10 vaccinators. The units would continue work in a locality until a number equivalent to 85–90% of the estimated population had been vaccinated. As in Afghanistan, the plans called for the teams to spend 24 consecutive days in the field, followed by 7 days' leave. A 10% sample of the vaccinations performed was to be assessed 1 week after vaccination. In addition to the surveillance–containment unit at regional level, a 10-man surveillance and containment unit was to be established in each district. The projected manpower required and the number available as at December 1968 are shown in Table 14.22.

Table 14.21. West Pakistan: plan for mass vaccination campaign—number of vaccinations to be performed each year, (thousands)

Health region	1968–1969	1969–1970	1970–1971
Lahore	12 200	3 600[a]	3 000[a]
Sargodha	14 700	4 400[a]	4 400[a]
Khairpur	[b]	6 800	2 000[a]
Hyderabad	[b]	8 300	1 900[a]
Peshawar	[b]	[b]	8 600
Quetta	[b]	[b]	1 400
Total	26 900	23 100	21 300

[a] Maintenance phase: vaccination of 30% of total population.
[b] Continuation of routine vaccination activities.

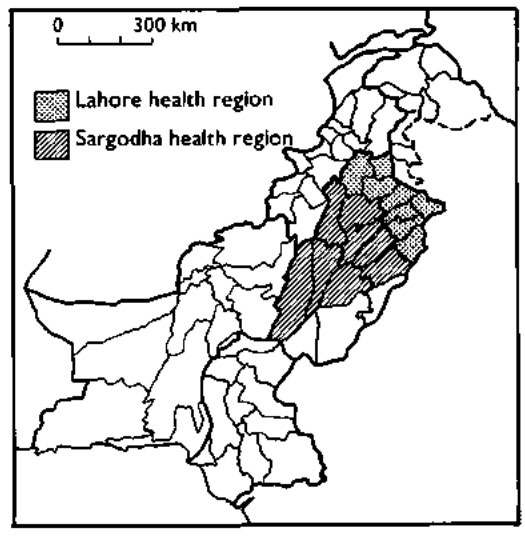

Fig. 14.10. Pakistan: districts to be vaccinated, 1968–1969.

Table 14.22. Pakistan: projected personnel requirements for the smallpox eradication programme, 1969

Personnel category	Number needed	Number available	Number to be recruited
Medical officers	22	22	0
Superintendents of vaccination	28	23	5
Assessors	80	40	40
Supply officers	19	6	13
Clerks and stenographers	46	22	24
Vaccinators	1 170	1 097	73
Others	47	27	20
Total	1 412	1 237	175

WHO agreed to provide US$200 000 in support of the programme, for the purchase of 25 Land Rovers, 125 motor cycles, 1300 bicycles, 25 refrigerators, a stock of bifurcated needles, and miscellaneous supplies. (Eventually WHO provided approximately US$1.3 million to the programme, as well as 70 million doses of vaccine (Table 14.23).) Freeze-dried vaccine produced at the Institute of Public Health, in Dhaka, East Pakistan, was to be used. It was calculated that the government of West Pakistan would need to increase its budget for smallpox eradication from 1 334 650 rupees to 2 728 480 rupees (US$278 800–570 000) for each of the 3 years of the Intensified Programme. It was expected that the previous level of financing would be adequate to cover the maintenance phase.

The findings and recommendations of the research group from Lahore did not become available until shortly after this plan was drawn up in August 1967. Even so, sufficient resources were foreseen in the plan to permit surveillance and containment activities of the type recommended.

Table 14.23. Pakistan: WHO support provided to the smallpox eradication programme, 1967–1978 (US$)

Year	Personnel and local costs	Supplies and equipment[a]	Total
1967[b]	222	200 858	201 080
1968[b]	15 542	58 305	73 847
1969[b]	24 610	89 187	113 797
1970[b]	32 534	96 834	129 368
1971[b]	49 355	17 886	67 241
1972	76 234	3 519	79 753
1973	61 444	123 166	184 610
1974	85 048	29 689	114 737
1975	67 306	109 025	176 331
1976	119 158		119 158
1977	48 520		48 520
1978		24 000	24 000
Total	579 973	752 469	1 332 442

[a] Excluding supplies of vaccine (about 70 million doses).
[b] WHO records reflect support given to both West Pakistan and East Pakistan (which became the independent state of Bangladesh in December 1971). Approximately half of the total was provided to West Pakistan and these are the figures shown in the table.

By December 1968 major problems had become apparent. The government did not increase the budget but, in fact, decreased it by 30%—to 1 million rupees. The plan envisaged the use of local body vaccinators as part of the complement of personnel but they were responsible to their own union councils (administrative units each responsible for a population of about 10 000) and the councils, in turn, to the Ministry of Basic Democracy. As the WHO adviser was to report: "A number of vaccinators have been appointed under political pressure and many of them are recommended by influential persons and are engaged in other duties or private jobs." Likewise, vaccinators in the municipal areas were under an entirely different jurisdiction, and there was no coordination of their activities with those of the provincial or regional staff. The problems of programme direction were further complicated when supervisory staff indicated that they could not travel to the field because the government's travel allowance was too meagre to cover the cost of even the most austere board and lodging. Last but not least of the difficulties was that no provision had been made for the purchase from programme funds of freeze-dried vaccine from the government's quasi-independent Dhaka laboratory. Up to this time, liquid vaccine had been purchased by union councils with their own funds and no administrative mechanism existed to permit these funds to be diverted to the purchase of freeze-dried vaccine.

One by one, the problems were solved or partially solved by a variety of means. Because vaccine production at the Dhaka laboratory was found to be inadequate to supply more than East Pakistan, WHO provided freeze-dried vaccine which had been contributed by various donors, primarily the USSR. WHO agreed to provide funds to supplement the travel allowance of national supervisory staff to permit them to travel to the field. The Ministry of Basic Democracy was, with difficulty, persuaded to issue an order to the union councils directing local body vaccinators to work with the programme, an order which was subsequently ignored as often as it was respected. Eventually, the national government authorized additional funds to recruit the requisite staff.

The programme in the 16 districts began in June 1969, but outside these districts no effort was made to develop reporting or surveillance activities. Even in the 16 districts, the so-called "fire-fighting" and surveillance teams did little. Indeed, in Lahore, one of the principal urban centres, a surveillance programme was not established until May 1972.

In all, some 1600 government staff participated in the unnecessary mass vaccination campaign in the 2 regions. The campaign was completed at the end of May 1970. One million primary vaccinations and 22 million revaccinations were recorded in a population of 27 million persons. Between March and May, 313 000 persons in 546 localities were examined to determine the level of vaccinial immunity achieved. The survey revealed that only 3.7% of them had neither a vaccination scar nor the pockmarks of smallpox. Even making allowance for possible errors in the assessment, it was apparent that the residual number of susceptible individuals was small but, as the research group from Lahore had shown, the number of unprotected persons had not been large when the vaccination campaign began. The marginal improvement was confirmed by a study in a division in which the health services were the least adequate: before the campaign, 10.5% of the population were found to be unprotected; after its completion, 8% remained unprotected.

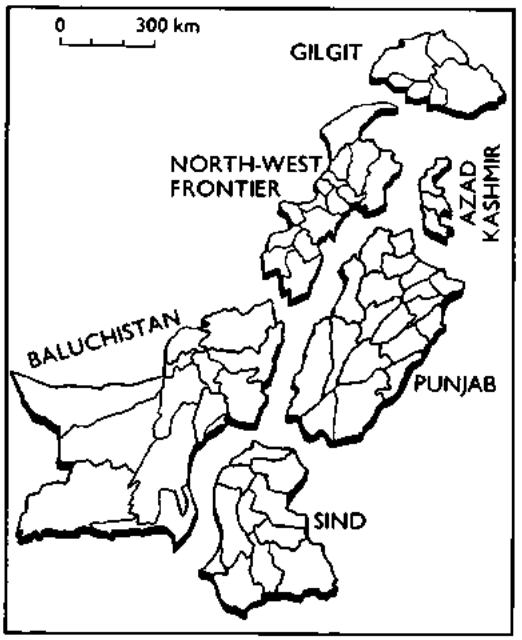

Fig. 14.11. Pakistan: provinces (or federally administered areas) and districts in July 1970.

One Programme Becomes Six, July 1970

On 1 July 1970, the administrative divisions of West Pakistan were abruptly changed by the government as part of the efforts to cope with increasing tensions in the relationships between East and West Pakistan. As has been mentioned above, the province of West Pakistan was divided into 4 independent provinces and 2 small, federally administered regions in the north of the country (Azad Kashmir and Gilgit) (Fig. 14.11). The populations of the provinces differed greatly in size: Punjab, 32.1 million; Sind, 11.9 million; North-west Frontier Province, 9.5 million; and Baluchistan, 1.6 million. The 16 districts in which the mass vaccination campaign had been conducted were all in Punjab Province, along with 3 additional districts. Early in the autumn of 1970, mass vaccination was completed in these 3 districts, during which an additional 200 000 primary vaccinations and 2.4 million revaccinations were reported to have been given. However, as shown in Fig. 14.12 and Table 14.24, the total of 25.6 million vacci-

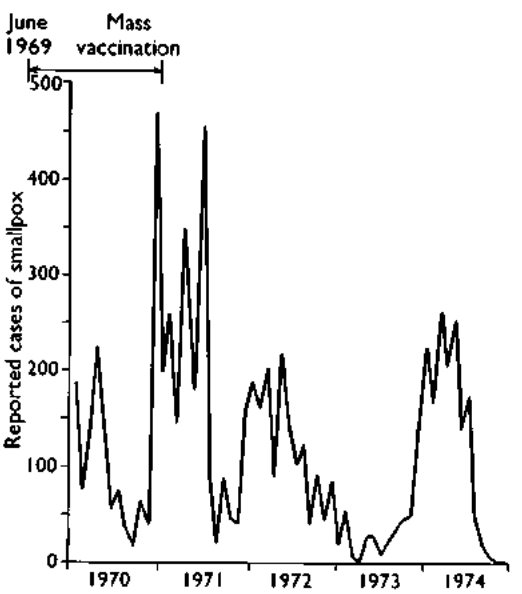

Fig. 14.12. Pakistan, Punjab Province: number of reported cases of smallpox, by month, 1970–1974.

Table 14.24. Punjab Province: number of reported smallpox cases by district, 1967–1974

District	1967	1968	1969[a]	1970[a]	1971	1972	1973	1974
Bahawalnagar	156	122	642	63	2	0	1	2
Bahawalpur	653	375	182	78	46	22	2	16
Campbellpur (Attock)	82	12	42	62	169	57	8	48
Dera Ghazi Khan	46	0	21	5	0	81	13	0
Gujranwala	68	6	22	340	702	192	10	93
Gujrat	40	5	30	18	47	0	8	26
Jhang	203	0	0	19	53	26	5	1
Jhelum	52	2	5	5	2	2	4	16
Lahore	2 175	79	444	197	216	418	220	601
Lyallpur (Faisalabad)	86	20	36	0	93	84	13	120
Mianwali	3	11	8	16	7	0	23	13
Multan	25	0	233	127	201	30	4	108
Muzaffargarh	45	0	3	19	41	151	36	77
Rahimyar Khan	70	239	126	26	8	273	5	8
Rawalpindi	48	12	13	340	164	0	0	32
Sahiwal	101	15	144	92	4	9	2	113
Sargodha	182	59	119	17	13	59	24	4
Sheikhupura	81	0	1	15	197	23	27	173
Sialkot	31	13	16	41	71	68	10	52
Total	4 147	970	2 087	1 480	2 036	1 495	415	1 503

[a] Mass vaccination campaign conducted during which 25.6 million vaccinations were performed.

nations performed in Punjab Province had little impact on the reported incidence of smallpox.

The failure of the campaign to have any apparent effect on the reported number of cases might be thought to reflect a better notification of cases, which masked the effect of the vaccination campaign. In fact, however, the surveillance teams functioned poorly and the notification system was not improved during this period.

Because of the subdivision of West Pakistan into 4 separate provinces and because each of the provinces was granted almost total autonomy in health matters, new provincial governments had to be persuaded of the need to undertake a smallpox eradication programme, to create some sort of organizational structure, to establish a budget and to recruit and/or assign personnel. In 3 of the provinces, no smallpox eradication activities had yet been undertaken. The national government and the national programme director had responsibility for the signing of agreements with WHO to permit advisers to be assigned and equipment to be provided, but had no authority over field activities except in the remote and sparsely populated Azad Kashmir and Gilgit.

The constraints on federal authority are illustrated by the frustration experienced in endeavouring to establish a vaccine production facility in the newly constructed national laboratories in the capital, Islamabad. In 1970 WHO offered to provide equipment for vaccine production and consultant assistance to establish a facility, which, it was hoped, would produce vaccine for the whole of West Pakistan. The federal government insisted that this could be done only if the government of Punjab transferred funds to the federal government that had previously been used to finance the now defunct liquid vaccine production unit at Lahore. After prolonged negotiation, agreement was reached and WHO ordered and delivered the production equipment. Because of Punjab's later refusal to honour the agreement, the equipment was never used. Vaccine for the programme continued to be provided by WHO, initially from various donors but after 1973, from the Pasteur Institute in Iran, which donated large amounts of vaccine to WHO.

In an effort to establish a programme encompassing the entire country, an interprovincial meeting was convened in December 1970 to seek the agreement of all provinces to undertake programmes. Two years had elapsed since the projected commencement of the programme in West Pakistan, but little had been achieved, except for mass vaccination in 19 districts. Meanwhile, the incidence of smallpox had remained virtually unchanged (Fig. 14.13). The lack of accomplishment after the expenditure of effort in districts with the most developed government and health structures and the greatest resources offered little encouragement for success at a national level.

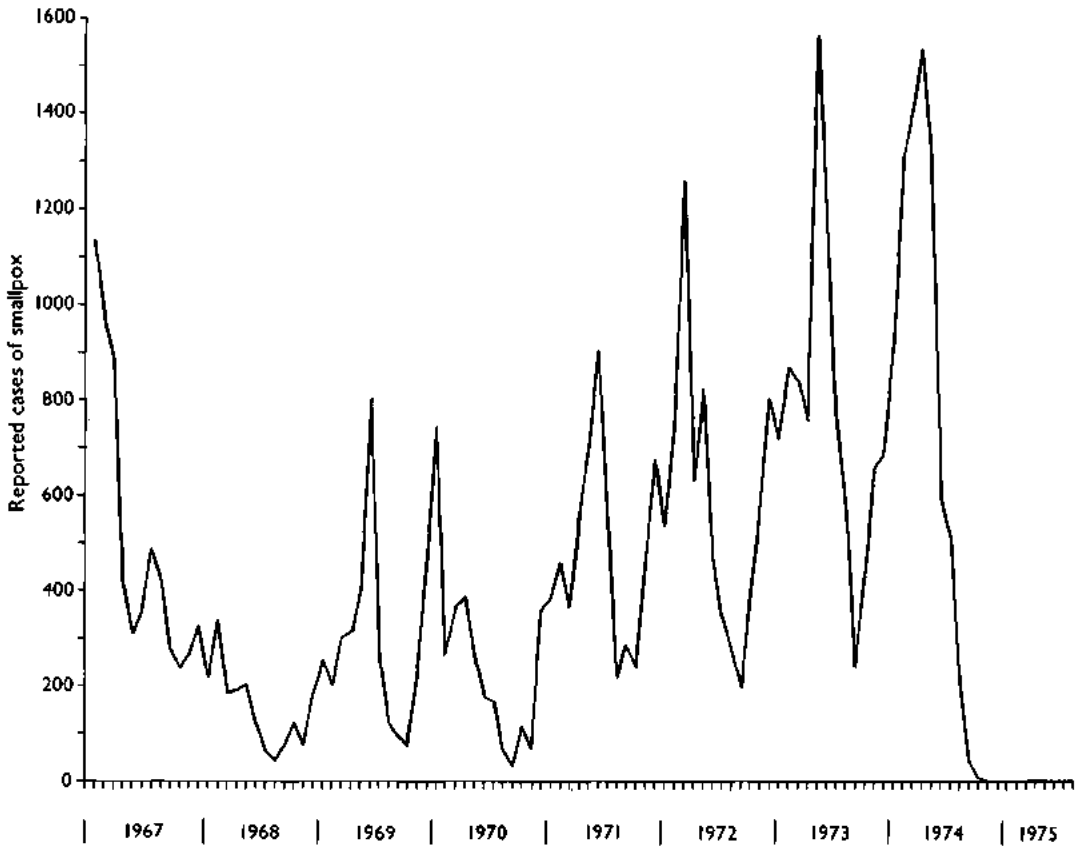

Fig. 14.13. Pakistan: number of reported cases of smallpox, by month, 1967–1974.

The Fourth Year of the Programme, 1971

At the meeting in December 1970, representatives of each of the provinces of West Pakistan agreed to give high priority to smallpox eradication: to create the necessary administrative structure, to develop a reporting and surveillance system and to seek the necessary funds for a systematic mass vaccination campaign. WHO agreed to recruit 3 additional advisers so that one could be assigned to each province, the senior adviser continuing in his capacity as national counterpart as well as adviser to the programme in Punjab. Additional supplies and equipment were ordered by WHO and travel allowances were provided for senior supervisors in all provinces. Meanwhile, because title to the vehicles and other equipment provided by WHO remained with the Organization, some supplies from Punjab Province were transferred to other provinces, an otherwise impossible action in the case of government-owned supplies.

It was agreed that interprovincial meetings would be held twice a year to coordinate the 4 separate programmes. However, each programme developed more or less independently, employing different strategies and achieving varying degrees of success. All of them encountered difficult obstacles, in the first instance because of the diversion of resources due to the civil war in East Pakistan, and then as a result of the tension between India and Pakistan at that time. In December 1971, when East Pakistan became the independent state of Bangladesh, these difficulties abated and additional resources were made available to all programmes. Three additional WHO advisers were recruited, arriving between March and June 1971. They were assigned, respectively, to Sind, North-west Frontier Province and Baluchistan. However, little was done during that year in Baluchistan, or in Sind except in the city of Karachi.

In 1971, Punjab Province appeared to be the best candidate to achieve the early interruption of transmission. Because 60% of the

population of West Pakistan lived in that province, it was believed that the interruption of transmission there would provide an impetus to the other provinces. A programme had been in operation for 3 years, the mass vaccination campaign had been completed, and few susceptible persons remained. The reporting system had improved little since 1968, but with the vaccination campaign finished, smallpox staff found themselves with few responsibilities other than to develop a surveillance–containment programme. In May, 8 assistant superintendents of vaccination and 19 vaccinators were trained in surveillance activities and began working in 2 teams under the direction of the Provincial Smallpox Eradication Officer, Dr M. B. Khawaja, who was succeeded by Dr Mohammed Rafique. In the summer of 1971, all district health offices were ordered to send weekly telegrams to report the number of cases discovered during the week. With 1407 health units (172 hospitals, 893 dispensaries, 39 rural health centres and 303 maternal and child health centres) in which cases might be identified, it was reasonable to expect that the reporting of outbreaks would be quite complete if a system could be developed.

Because there were only 2 large teams engaged in search and containment in a province of 32 million people, and because telegraphic reports were then being received from less than half of the districts despite the provincial order, many outbreaks continued to be overlooked. More important, little was done in urban areas—the chief foci for the dissemination of smallpox. Programmes in the urban areas were the responsibility of the municipal corporations, each of which had its own health structure, and these, independent of provincial policies and supervision, continued to carry out traditional routine vaccination campaigns.

During 1971, the Punjab surveillance teams investigated 81 outbreaks, in which 561 cases had been reported; an additional 1475 cases were discovered. Although the total of 2036 cases was the same as that recorded in 1969, when the vaccination campaign began, the number of cases declined sharply in the latter half of the year, only 20–90 being reported monthly between July and November.

Meanwhile, in North-west Frontier Province, an energetic WHO adviser, Dr G. P. Marchenko, arrived in March 1971. With the help of an able provincial medical officer, Dr Mohammed Ayaz Khan, the province launched a mass vaccination campaign in May in 4 of its most populous districts—Peshawar (the capital), Mardan, Hazara and Swat. In contrast to Punjab, case detection was specifically emphasized as an important component of activity. Numerous cases were discovered by the vaccination teams (Table 14.25; Fig. 14.14). By the end of the year, 2654 cases had been detected, most of which (2132) were in the 4 districts in which the campaign was being conducted. This was 5 times the number recorded during the preceding year. The

Table 14.25. North-west Frontier Province: number of reported cases of smallpox, by year and by district, 1971–1974[a]

District	1971	1972	1973	1974
Bannu	187	119	0	0
Chitral	3	0	0	0
Dera Ismail Khan	183	96	0	3
Dir	0	0	0	7
Hazara	113	19	9	127
Khyber	18	29	51	0
Kohat	86	20	0	0
Kurram	0	0	50	0
Malakand	27	0	0	0
Mardan	473	62	3	0
Peshawar	1 492	963	79	0
Swat	54	10	2	26
Waziristan	13	20	0	0
Unknown	5	0	0	0
Total	2 654	1 338	194	163

[a] No cases were reported from Mohmand District.

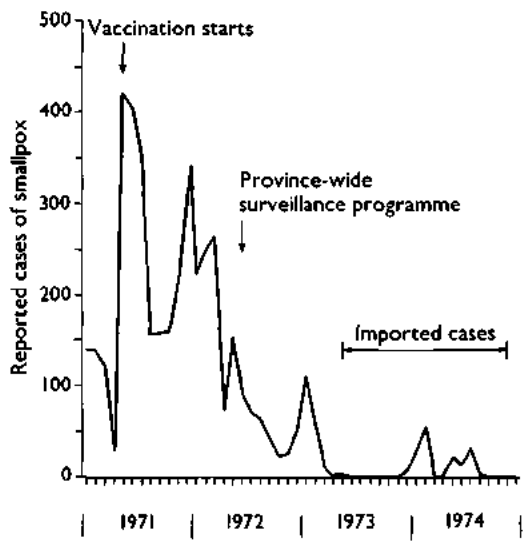

Fig. 14.14. Pakistan, North-west Frontier Province: number of reported cases of smallpox, by month, 1971–1974.

"epidemic" alarmed provincial authorities but stimulated political interest and support, which continued throughout the rest of the programme.

Commencement of Country-wide Activities, 1972

During 1972, smallpox eradication programmes were introduced in Sind and Baluchistan Provinces and activities at last extended throughout most of the country. The provincial programmes progressed at different speeds and encountered such different problems that each is described separately. The remarkably successful programme in North-west Frontier Province is dealt with first. Transmission was interrupted only 2 years after the programme had begun, but the area was inundated by importations from the other 3 provinces for more than a year thereafter. Next to be discussed is the programme in Punjab, with its large population and attendant operational problems, and then the inadequately supported and poorly organized programmes in Sind and the sparsely populated Baluchistan. Table 14.26 shows the number of reported cases by year for each of the provinces during the period 1970–1975.

North-west Frontier Province

North-west Frontier Province extends from the foothills and mountains of the Himalayas along the border with Afghanistan to the plains of the Indus river in the east and south-east (Fig. 14.15). About three-quarters of the population are traditionally independent Pathans, some of whom at that time enjoyed semi-autonomy in federally administered tribal areas in the mountainous districts of Waziristan, Khyber, Kurram, Malakand and Mohmand. Extensive vaccination campaigns had been conducted during the preceding years throughout the plains and foothills, as in Punjab, but in some sparsely settled mountainous and tribal areas variolation continued to be practised.

The house-to-house vaccination campaign, which began in May 1971 in 4 districts, was completed in June 1972. A staff of 350 persons vaccinated 3.6 million people (about 80% of the 4.4 million inhabitants of the area). Initially, the search for cases and the containment of outbreaks were limited to these 4 districts. In July 1972, vaccination campaigns were initiated in the districts lying in the Indus river plain (Kohat, Bannu and Dera Ismail Khan) and efforts were made to launch

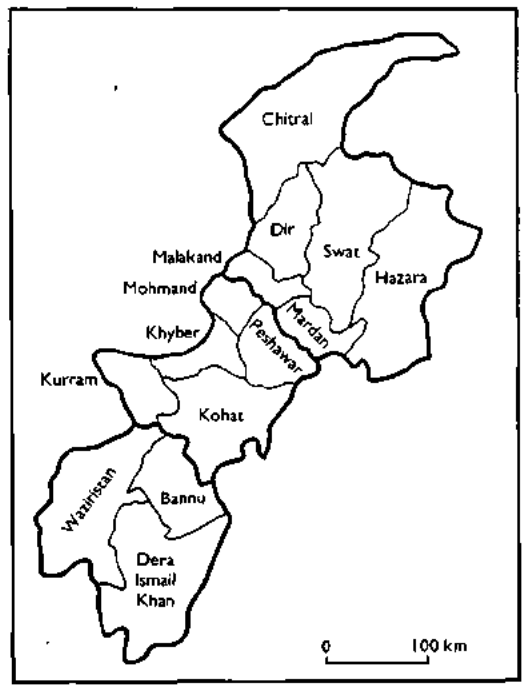

Fig. 14.15. Pakistan: districts of North-west Frontier Province, 1973.

Table 14.26 Pakistan: number of reported cases of smallpox, by province, 1970–1975

Year	Pakistan, total	Punjab	Sind	Baluchistan	North-west Frontier	Azad Kashmir
1970	3 192	1 480	1 107	80	525	0
1971	5 808	2 036	827	291	2 654	
1972	7 053	1 495	3 661	559	1 338	0
1973	9 258	415	7 848	801	194	0
1974	7 859	1 503	5 982	202	163	9
1975	0	0	0	0	0	0

campaigns in the tribal agency districts. The latter were soon abandoned, however, when it was discovered that frequently only 5% or less of the population would accept vaccination. Data on the efficacy of the vaccination campaign are available from surveys conducted in 1973 in 5 districts. The results were, in general, comparable to those in Punjab (Table 14.27).

Simultaneously with the beginning of a vaccination campaign in the Indus river plain, case detection and outbreak activities were extended throughout the province. Six "fire-fighting" teams, each with a vehicle, were trained and assigned responsibility for designated districts to improve case notification and to detect and contain outbreaks. Meanwhile, in Peshawar, the capital, 20 teams of 2 persons each began a house-to-house search for cases. When cases were discovered, an 8-man team carried out containment vaccination. For the first time in Pakistan, the strategy which had been recommended 5 years earlier by the Pakistan Medical Research Centre team was finally to be implemented.

The number of cases steadily decreased during the late spring and throughout the summer—the seasonal low point in smallpox transmission—and from October to the end of December, only 100 cases were discovered, of which 98 were in Peshawar District. The outbreaks all occurred near Peshawar City, in small villages frequented by smugglers from the tribal areas. None of the outbreaks was large but containing them proved difficult because the villages were considered to be dangerous, especially at night, and the villagers often refused to provide information about cases. Additional impetus was given to the programme, however, when in November a new WHO adviser arrived—Dr Reinhard Lindner, who had played an important role in developing the surveillance–containment strategy in Indonesia. Gradually, the problem in Peshawar came under control, and in April 1973 the last cases occurred in that district.

Table 14.27. North-west Frontier Province: results of vaccination scar survey in children under 15 years of age in 5 districts, August 1973

District	Number examined	% with scar, by age group (years)		
		<1	1–4	5–14
Bannu	3 360	34	92	99
Kohat	2 016	49	95	98
Kurram	2 016	55	94	99
Peshawar	4 872	50	91	97
Mardan	4 032	69	94	98

Meanwhile, cases began to be reported in January 1973 in the tribal areas of Kurram and Khyber, probably introduced from Peshawar. The teams were permitted to enter the area only with a military guard and only after assuring tribal leaders that they would not vaccinate them but would merely document the numbers of cases and deaths. In all, 101 cases were recorded in the outbreaks. Fortunately, smallpox transmission ceased spontaneously, probably in response to the traditional practice in villages of isolating cases and permitting only those previously infected with smallpox to care for the patients.

During the first 6 months of 1973, the only cases detected in the entire province apart from those in Peshawar and the Kurram–Khyber tribal area were 2 imported into Mardan from Punjab Province in January, and 2 in Swat notified in May following an importation from Karachi. By May, it appeared that transmission had been interrupted. The vaccination campaign was stopped and the vaccinators were assigned solely to a search for cases. A reward of 25 rupees (US$2.50) was offered to anyone who detected a case. Numerous rumours were investigated but no cases were found. In October, the reward was doubled.

In November, however, importations began, primarily from Punjab but also from Sind and Baluchistan. Between November 1973 and September 1974, 35 outbreaks and 173 cases occurred. Of 34 outbreaks for which a specific source could be identified, all could be traced to Punjab, except 3 from Sind and 1 from Baluchistan. All but 3 of the cases were in the northern districts of Hazara (136 cases), Swat (26 cases), Dir (7 cases) and Mardan (1 case). The province's final outbreak of 3 cases occurred in the southern district of Dera Ismail Khan, the last on 7 August 1974. Subsequent extensive search and a reward which was progressively raised to 200 rupees, then to 500 rupees and finally to 1000 rupees failed to uncover further cases.

Only partial data are available regarding the age distribution and vaccination status of cases in the province (Table 14.28).

As in Afghanistan, only a small proportion of cases occurred among adults, of whom, however, one-third had scars indicating previous vaccination. Fifty-eight percent of the

Table 14.28. North-west Frontier Province: number of reported cases of smallpox, by age and by vaccination status, 1970–1974

Age group (years)	Cases[a]		Number with known vaccination status	Number vaccinated	% vaccinated
	Number	%			
<1	289	9	275	25	9
1–4	1 605	49	1 556	171	11
5–14	1 064	33	1 032	185	18
⩾15	303	9	281	91	32

[a] Data not available for 1613 cases.

cases occurred in children under 5 years of age, and although 10% were reported to have been vaccinated before onset, in some instances vaccination had been performed late in the incubation period during containment vaccination.

The achievements of the programme in North-west Frontier Province were notable. In April 1973, less than 2 years after the start of activities, transmission was interrupted, despite a health structure inferior to that of either Punjab or Sind Province, despite the greater difficulties of transport and communication and despite the existence of large population groups which refused vaccination. One might suppose that the authorities of other provinces would have found its programme and strategy instructive but, in fact, they openly doubted the reported results. In rancorous interprovincial meetings, they expressed scepticism and denounced the authorities of North-west Frontier Province for asserting that after April 1973 the only cases of smallpox that had occurred there had been imported from their provinces. Most adamant and vocal were representatives from Punjab Province.

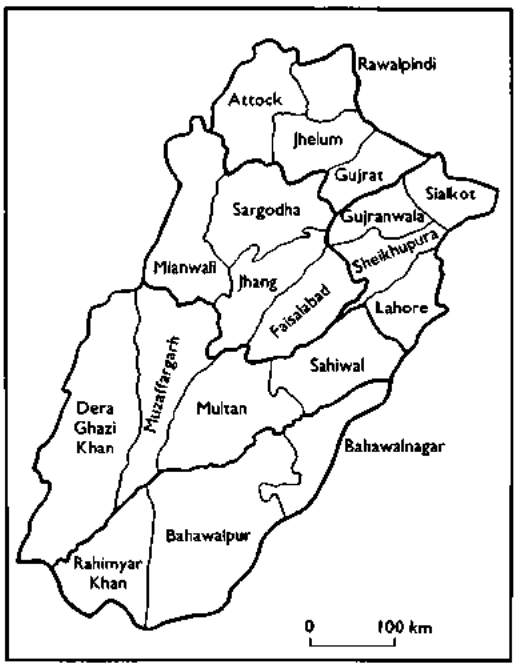

Fig. 14.16. Pakistan: districts of Punjab Province, 1973.

Punjab Province

During 1972, Punjab Province strengthened its surveillance programme. Instead of 2 large surveillance groups, more surveillance teams of smaller size were created, each of which travelled extensively to improve reporting from the districts (Fig. 14.16) and to search for cases village by village. In all, 1495 cases were detected, 500 fewer than in 1971, when reporting was far less complete. Outbreaks were detected and contained reasonably quickly—73% being detected within a month of onset and 97% within 2 months.

Little was done in urban areas, however, until May 1972, when special measures were taken to control smallpox in Lahore, the provincial capital. In the municipal corporation, 75 vaccinators were then working in 34 vaccination centres, only rarely leaving these centres to vaccinate people in the surrounding community or to detect and contain cases. It was agreed that a WHO adviser would be assigned to work in the corporation and, in May 1972, 6 sanitarians were trained in methods of case detection. One each was assigned to 4 sectors of the city and 2 were retained at headquarters to investigate cases brought to the infectious disease hospital.

Each of the 34 vaccination centres was designated a primary reporting unit, which would send reports weekly, and 51 of the 75 vaccinators were assigned to a house-to-house search for cases; a special containment team of 10 vaccinators was stationed at the provincial office. A report prepared in October documented 314 cases in 52 outbreaks in Lahore District, primarily in slum areas around the perimeter of the city. Almost one half (41.4%) of the cases were detected within 2 weeks of onset and 72% within 1 month. Only 4 outbreaks were traced to importations from other districts and these resulted in a mere 7 cases. However, numerous outbreaks, originating in Lahore, were identified during 1972 in other districts in the central and northern parts of the province. Indeed, between July and September, 37% of all cases in Punjab could be traced to Lahore. Cases in the city continued to occur primarily among unprotected persons, who had been found, in a 1969 survey, to constitute only 6.9% of the total population (Ali & Heiner, 1971). Although immigration may have increased the proportion of susceptible persons somewhat during the 3 succeeding years, a continuing vaccination campaign served to sustain vaccinial immunity. Attack rates among contacts in infected households substantiated the fact that those who had previously been vaccinated were at significantly less risk than the unvaccinated (Table 14.29).

The importance to the province of controlling smallpox in Lahore had long been pointed out and this was fully substantiated when an effective programme was finally begun. Coincidentally with a decrease in incidence in Lahore, the number of reported cases of smallpox in Punjab, as well as in neighbouring North-west Frontier Province, fell sharply during the summer of 1972 and continued to decline during the autumn and winter months.

The programme was so successful that during March 1973, at the time of highest seasonal transmission, only 2 cases were detected in Lahore and only 8 in the entire province of Punjab. The Provincial Director of Health Services decided that the programme had succeeded and decentralized the surveillance operation. The Provincial Director of the Smallpox Programme was informed that he should undertake no further field travel and the WHO vehicle assigned to him was given to another medical officer. Each of the 5 divisional deputy directors of health services was assigned responsibility for one of the surveillance teams, and they in turn directed the teams to undertake other duties, primarily cholera vaccination. Surveillance in Lahore effectively ceased.

Through late October, the reported incidence of smallpox remained low; in fact, from 2 September to 20 October, no cases whatsoever were reported in Lahore District. It was the calm before the storm (Fig. 14.17). In late October smallpox outbreaks were again detected in Lahore, although investigations revealed that the city had, in fact, never been free of the disease. During December small-

Table 14.29. Lahore: frequency of cases of smallpox among, vaccinated and unvaccinated contacts, by age group

Age group (years)	Unvaccinated contacts			Vaccinated contacts		
	Number	Number of cases	%	Number	Number of cases	%
<1	36	15	41.7	11	3	27.3
1–4	111	74	66.7	79	3	3.8
5–14	78	58	74.4	258	14	5.4
≥15	30	12	40.0	414	10	2.4
Total	255	159	62.4	762	30	3.9

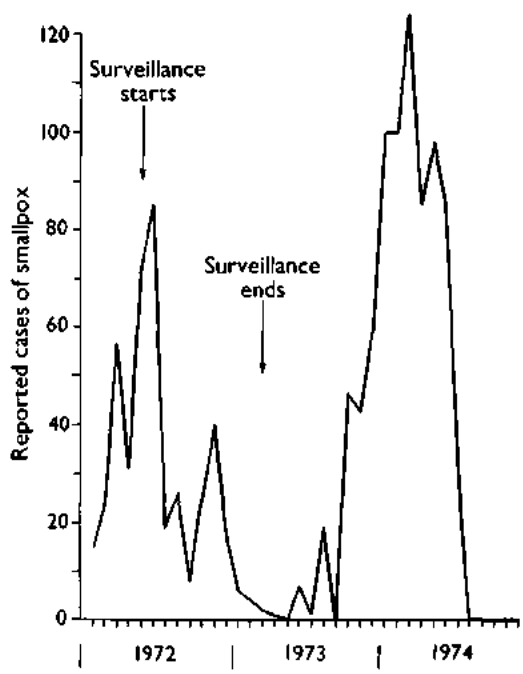

Fig. 14.17. Pakistan, Lahore District: number of reported cases of smallpox, by month, 1972–1974.

pox spread widely through the city and cases began to appear in other districts and in North-west Frontier Province. By the end of December, 8 districts of Punjab had recorded outbreaks.

Despite the enormous resources and energies that had been devoted to the programme in Punjab, the situation had deteriorated to such an extent that conditions were not much better than they had been before the initiation of the mass vaccination campaign more than 5 years earlier. As at December 1973, the provincial smallpox eradication programme, such as it was, consisted of 4 wholly independent and uncoordinated components: (1) the Provincial Smallpox Eradication Officer with 8 assistant superintendents of vaccination and 14 surveillance agents; (2) 5 divisional surveillance teams under the direction of deputy directors of health services; (3) 19 independent district health offices, each with supervisors and vaccinators—some 1200 persons in all; (4) the municipal corporations, with their separate staffs.

It had been demonstrated beyond question in North-west Frontier Province that smallpox transmission could be interrupted even in difficult areas if the available resources were effectively managed. The problem in Punjab was to obtain an adequate political commitment, an appropriate strategy and a stability of leadership for long enough to permit this to be done.

Three events ultimately provided the necessary stimulus to a political commitment. The first was the recording in 1973 of 9258 cases of smallpox, the country's highest total since 1948. Although this could be attributed to more complete notification, the political authorities were alarmed and began both to query the performance of health officials and to make greater resources available. The second event was the interruption of transmission in Afghanistan in 1972, which caused some embarrassment in Pakistan. Afghanistan, considered to be a far less developed country, pointedly and repeatedly indicated to the Pakistani authorities that all its cases since mid-1972 had resulted from importations from Pakistan. The third incident was India's decision in the summer of 1973 to mobilize its vast resources of health manpower to undertake monthly village-by-village searches to detect and contain outbreaks throughout the country. Optimistically, the Indian government forecast that the interruption of transmission would occur between January and June 1974. With Bangladesh and Nepal making excellent progress, it appeared that by late 1974 Pakistan might well be the last reservoir of smallpox in Asia.

Manpower in Punjab was not a problem but leadership and management were. A change occurred in February 1974 with the arrival of a new WHO adviser—Dr Omer Sulieman, the dynamic former director of the successful eradication programme in the Sudan. Within weeks, a moribund programme began to revive, and only 10 months later Punjab recorded its last case.

On his arrival in Lahore, Dr Sulieman reported on the situation: no plan or targets had been committed to paper; the concept of surveillance was accepted in principle but ignored in practice; officials continued to insist that vaccination targets should be met in all areas; there was no search for cases; containment was poor; and cooperation between different groups was so lacking that even data regarding cases were not forwarded to the provincial office.

The Secretary of Health extended full support and ordered district and municipal corporations to cooperate with the programme. A written document establishing guidelines and technical commitments was prepared and distributed; surveillance teams were reconstituted and trained; a reward of 10 rupees for each new outbreak reported was announced; and vaccinators were asked to search for cases among the groups of people they vaccinated. To intensify the search, population planning and malaria eradication staff were directed to undertake a house-to-house search for 1 week each month. When it was found that women were better received by the people and were more effective in searching for cases, 12 000 were employed between February and May; most of them were traditional birth attendants or municipal sweepers. In addition, during March, a special 2-day house-to-house search was conducted in Lahore by 50 000 schoolchildren and their teachers. They discovered 1800 persons with rash and fever of whom 13 were suffering from previously undetected smallpox.

Between February and May, substantial progress was made in the detection and containment of outbreaks but the smallpox incidence remained high. This was due, in part, to more complete reporting and, in part, to the high seasonal transmission. By June

1974, it was apparent that the cities of Lahore, Multan and Lyallpur (Faisalabad) were the key problems, accounting for the majority of cases and representing the source of infection of many rural outbreaks. In these cities, containment activities were strengthened, in line with the procedure then operating in India, by assigning a supervisor and 3 vaccinators to each outbreak to list and to vaccinate all residents and to stay in the area to vaccinate visitors until the outbreak was controlled. A vaccinator was also posted at each infected house until the last case had recovered. Efforts were also made to find and vaccinate all relatives, wherever they resided.

Whatever their instructions, some district health officers continued to rely on vaccination rather than surveillance and so, in June, routine vaccination was officially suspended and vaccinators were assigned solely to search and containment activities. To improve coordination, the Secretary of Health began to hold monthly meetings with all district health officers to emphasize his personal concern. In July, the health officers were relieved of other official duties in order to supervise a village-by-village search programme which covered one-third of the province's 23 692 villages each month. This programme was similar to that which had begun in India almost a year before.

With a declining number of cases and outbreaks—partly because of better control activities and partly because of the seasonal decline in smallpox incidence—it was possible to exercise better supervision in each remaining outbreak. Careful efforts were made to trace the source of cases and containment was tightened. Finally, on 16 October 1974, the last case of smallpox in Punjab, and in Pakistan as a whole, occurred in Multan City. The search continued, enhanced by the offer of a growing reward, but no further cases were found.

In Punjab, less than 10 months had elapsed since the introduction of the first well-coordinated province-wide programme of surveillance–containment and the occurrence of the last case. However, almost 6 years had passed since the beginning of the programme.

Baluchistan Province

Until 1972, little was achieved in the eradication programme in Baluchistan, the most sparsely populated and least developed of Pakistan's 4 provinces. It occupies 40% of Pakistan's land area and is composed of desert and rolling hills with few roads. Only 10% of the land was arable, most of it being in the eastern districts, in which the population was concentrated (Fig. 14.18). Baluchistan was a new province, created in July 1970, and the government structure was only beginning to take shape. Communication and travel were difficult; the postal service was all but non-existent; and fewer than 100 physicians were employed there. Vaccinial immunity in Baluchistan was substantially lower than elsewhere in Pakistan, as was demonstrated by a scar survey performed in 1976 in 3 of the districts in which health services were the best (Table 14.30).

A mass vaccination campaign began in 1971 in the more populous north-eastern area of Quetta, Pishin and Zhob, employing some 30 vaccinators and some 20 support and supervisory staff. In fact, little was achieved, the numbers of recorded vaccinations for the province actually showing a decline, from 549 000 in 1970, to 422 000 in 1971.

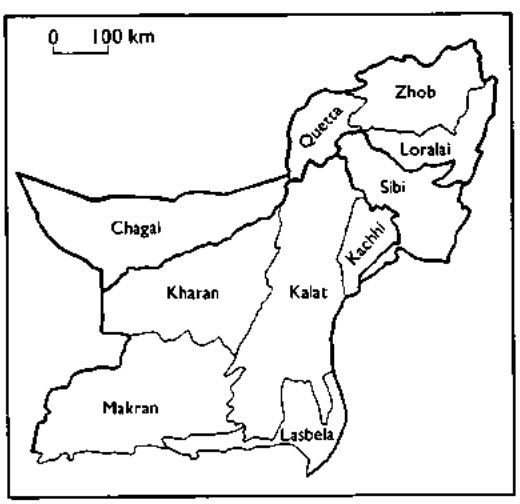

Fig. 14.18. Pakistan: districts of Baluchistan Province, 1973.

Table 14.30. Baluchistan: results of vaccination scar survey, in children 5 years of age and under, 1976

District	Number of villages	Number examined	% vaccinated	
			Under 2 years	2–5 years
Loralai	19	719	23	40
Quetta	6	78	0	29
Zhob	17	997	15	59
Total	42	1794	17	50

In May 1971, a WHO adviser was assigned to the province, but the difficulties of maintaining even a few vehicles in operation in the field proved formidable. In the latter part of 1971 and in 1972, some outbreaks were investigated and vaccinations performed in and around Quetta, the capital, but little progress was made until the summer of 1972, when it was decided that a mass vaccination campaign was not feasible and the effort was abandoned. Surveillance agents were then posted to each district and 5 mobile teams, each composed of 4 persons, were constituted; 2 of these undertook a search for cases and 3 performed vaccinations in what were considered to be vulnerable areas. The number of reported cases increased from 80 in 1970 to 291 in 1971 and to 559 in 1972 (Table 14.31). Cases were reported from each of the 10 districts in 1972, but most of them (444) were in Quetta and the nearby town of Sibi, in which the mobile teams were working. In all, the teams themselves detected 486 (87%) of the cases.

The surveillance programme futher improved following the arrival in February 1973 of an experienced WHO adviser, Dr P. R. Arbani, a national of Indonesia who had worked in the smallpox eradication programme in that country. By July, weekly reports of cases began to be received routinely from all districts. With improved training and increasing involvement of the few existing district and local health staff, cases were detected more quickly and were better contained. During 1973, 165 outbreaks with 801 cases were documented. With the exception of 2 cases in Chagai, all cases were reported from the more populous north-eastern districts.

Table 14.31. Baluchistan: number of reported cases of smallpox, by district, 1970–1974

District	1970	1971	1972	1973	1974
Chagai	0	1	2	2	0
Kachhi	0	2	28	399	1
Kalat	7	11	44	25	115
Kharan	14	0	3	0	0
Lasbela	0	17	10	0	0
Loralai	0	31	8	21	0
Makran	10	16	1	0	0
Quetta	41	76	183	75	84
Sibi	2	135	261	256	2
Zhob	6	2	19	23	0
Total	80	291	559	801	202

By 1974, the surveillance programme was functioning far more effectively. Only 40 outbreaks with 202 cases were discovered during that year, of which 27 were detected within 2 weeks of onset; 30 of the 40 outbreaks consisted of only 1 or 2 cases (Tables 14.32 and 14.33). The last 4 outbreaks (of 2, 18, 23 and 65 cases respectively) occurred in Baluchistan in the summer of 1974 and were associated with variolation in Kalat District. Although the outbreaks were quickly detected, many cases among variolated children were already late in the incubation period before the team arrived.

Smallpox Transmission on Public Transport

Variola major was usually transmitted within the confines of a building, primarily in a household and sometimes in a hospital. Public transport was rarely implicated. This was because patients usually experienced a severe prodromal illness before developing rash and being able to transmit infection. Fortunately, few people travelled on public transport after first becoming ill but, if they did, infection could be disseminated rapidly and widely. One such episode occurred in Loralai District, Baluchistan, in July 1972.

On 21 July, a 4-year-old girl, accompanied by her mother, travelled 55 kilometres on a crowded bus to a medical clinic in Loralai town, returning home the same day. The girl had fallen ill with smallpox on 1 July and had become progressively worse, developing a confluent rash. She died only 2 days after the bus trip. On the bus, the girl and her mother rode in the front on one of 5 seats set aside for female passengers and separated by a partial partition.

Five persons, exposed on the bus, subsequently developed smallpox: the 60-year-old bus driver and 4 girls ranging from 3 to 8 years of age. Four additional persons, exposed at the clinic, also developed smallpox. As a result, outbreaks developed 2 weeks later in 12 different villages over a distance of 65 kilometres. Thirteen additional cases occurred before the outbreaks were contained. (WHO/SE/72.41, Suleimanov & Mandokhel.)

Table 14.32. Baluchistan: interval between onset of first case of smallpox and detection of outbreak, 1973–1974

Year	Number of outbreaks detected within:				
	1 week	1–2 weeks	2–3 weeks	≥3 weeks	Total
1973	50	47	21	47	165
1974	16	11	2	10	39[a]

[a] Information not available for 1 outbreak.

Table 14.33 Baluchistan: number of cases of smallpox in outbreaks, 1973–1974

Year	1 case	2 cases	3–10 cases	>10 cases
1973	76	24	52	13
1974	23	7	6	4

After April 1973, all cases and outbreaks occurred near Quetta, in which the isolation ward of the civil hospital served as the principal focus for the dissemination of infection. In addition to being the source of Afghanistan's final outbreak, mentioned earlier, the hospital was the focus of infection of 25 additional outbreaks over a 3-year period (including the last 4 outbreaks in Quetta), all of which were traced to patients who had contracted the infection there. Despite continuing efforts by provincial smallpox eradication staff to persuade the responsible hospital authorities to isolate patients and to vaccinate all persons admitted to the hospital, here, as at so many other hospitals, little was done until smallpox eradication staff were assigned to perform these duties.

Baluchistan recorded its last case on 30 August 1974. An extensive search was then organized throughout the vast, sparsely settled desert areas of its western provinces but no cases were found. Transmission had been successfully interrupted in less than 2 years after a surveillance programme had begun—and without benefit of a mass vaccination campaign. The costs were low. The total expenditure by the government over a 3-year period from mid-1971 to mid-1974 was 610 000 rupees (US$61 500), or US$0.24 per head of population.

Fewer than one half of the cases in Baluchistan were among children under 5 years of age; one-fifth were among persons aged 15 years and over (Table 14.34). The generally older age distribution of cases reflects the occurrence of smallpox in comparatively isolated population groups among whom, in contrast to the situation in Afghanistan, variolation had not been widely practised in recent years.

The Last Outbreak in Baluchistan

Four weeks had elapsed without the reporting of a case in Baluchistan, when, on 1 August 1974, the assistant commissioner of a subdistrict reported to the district health officer in Kalat that he had heard rumours of smallpox in the area. A team immediately went to investigate and discovered cases in 4 villages (population 585) located at the top of a mountain, accessible only on foot. The first case had been exposed at Quetta's civil hospital in May and had become ill on returning home. On 4 June, a variolator was summoned; he took scabs from the patient and variolated the residents of the 4 villages. Between 4 June and 15 August, there were 108 cases and 9 deaths, as shown in the following table:

Age group (years)	*Natural infection*		*Variolation*	
	Number of cases	*Number of deaths*	*Number of cases*	*Number of deaths*
<1	0	0	3	2
1–4	2	0	19	0
5 14	3	0	26	0
≥15	11	2	44	5
Total	16	2	92	7

None of those infected had ever been vaccinated. Although the inhabitants of the 4 infected villages had a low level of vaccinial immunity, 90% of the people in surrounding villages were found to have been vaccinated.

Table 14.34. Baluchistan: number of reported cases of and deaths from smallpox and case-fatality rates, by age group, 1971–1974

Age group (years)	Cases		Number of deaths	Case-fatality rate (%)
	Number	% of total		
<1	155	8	42	27
1–4	617	33	114	18
5–14	697	38	85	12
⩾15	365	20	53	15
Unknown	19	1	6	
Total	1 853	100	300	16

Sind Province

In Sind Province, which mainly comprises a flat alluvial plain, 40% of the population lived in urban areas, including the cosmopolitan city of Karachi (Fig. 14.19). It was comparable to Punjab in the extent of its health programmes and personnel and in the availability of transport and communication facilities. In all, Sind had 120 hospitals, 918 dispensaries, 103 rural health centres and subcentres, and 116 maternal and child health clinics. In 1972, vaccinial immunity was found by survey to be over 95% in Karachi, and although lower in the rural areas, generally speaking it was probably comparable to that in Punjab and much better than that in Baluchistan or in North-west Frontier Province.

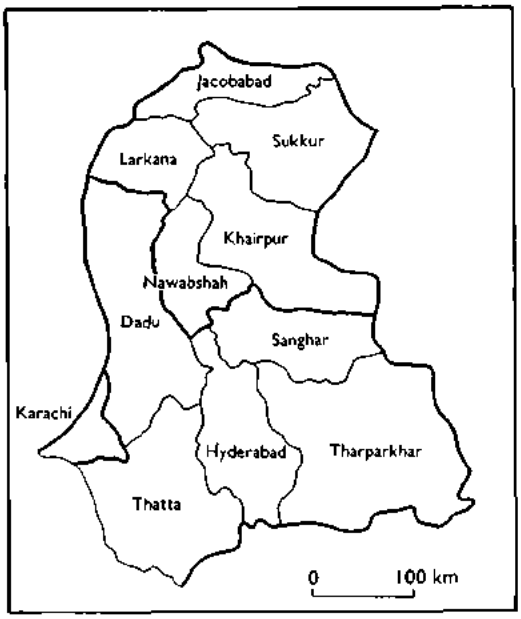

Fig. 14.19. Pakistan: districts of Sind Province, 1973.

Except in Karachi, the smallpox eradication programme was effectively ignored until the autumn of 1972. Early in 1971, the Karachi city authorities consolidated into a single organization the vast numbers of vaccinators who had been employed by a variety of different administrative jurisdictions, to undertake systematic vaccination and a programme of case detection. Three, later 6, surveillance teams and 3 containment teams complemented this effort, which proved so successful that between July and September 1971 no smallpox cases were found in the city. A week-long, city-wide search in mid-November confirmed the absence of cases. Karachi, however, was Pakistan's largest city and principal seaport and numerous travellers from all over the country passed through it. Most of them were from other parts of Sind in which the smallpox incidence was probably higher than anywhere else in Pakistan. Importations led to a number of cases (369 in 1972, 335 in 1973 and 252 in 1974), and some outbreaks in other parts of Pakistan were traced to Karachi. However, smallpox in Karachi remained a minor problem in comparison with the situation in Lahore.

Provincial health authorities exhibited little interest in the programme until the autumn of 1972. The existing smallpox eradication staff of 724 persons, including 644 vaccinators (1 for every 23 000 persons) continued a routine vaccination campaign during which 3–4 million people were reported to be vaccinated annually. Reluctantly, the provincial authorities had agreed to the assignment of a WHO adviser, Dr M. Chamsa, who arrived in June 1971. Efforts had been made to mount a special vaccination campaign but lack of government support soon caused the attempt to be abandoned, and attention was focused on surveillance. With only limited resources available, this commenced in the autumn of 1972. Outbreaks were soon detected in every district—727 in all, with 3661 cases (Table 14.35)—4 times the number of cases reported during the previous year. Even so, weekly reports were not received from all districts, nor was an active search for cases begun until late in 1972.

By the autumn of 1972, national and WHO staff had become increasingly concerned about the inadequacy of the Sind programme and the lack of interest on the part of the health authorities. By that time, the smallpox

Table 14.35. Sind Province: number of reported cases of smallpox, by district, 1970–1975

District	1970	1971	1972	1973	1974	1975
Dadu	0	18	108	296	48	0
Hyderabad	9	0	31	1 265	3 232	0
Jacobabad	7	70	314	788	7	0
Karachi	507	390	369	335	252	0
Khairpur	32	61	625	843	45	0
Larkana	105	55	538	1 260	56	0
Nawabshah	38	0	404	598	259	0
Sanghar	2	0	101	625	325	0
Sukkur	397	233	1 081	961	68	0
Tharparkar	10	0	89	728	1 472	0
Thatta	0	0	1	149	218	0
Total	1 107	827	3 661	7 848	5982	0

incidence was declining rapidly both in Punjab and in North-west Frontier Province. The programme in Baluchistan was proceeding slowly, but since the population of the province amounted to only 1.9 million, it was of less concern. In Sind, which was much more densely populated, an effective programme was vital. Accordingly, in November 1972, WHO convened a special seminar in Karachi in which provincial officials from all over Pakistan participated, together with smallpox eradication officers from other countries in the Eastern Mediterranean Region. The site had been deliberately selected in the hope of awakening the interest of senior officials in Sind. Henderson observed in his opening remarks:

"As for Sind, the considerable delay in initiating the programme and the many administrative problems encountered leave more yet to be done in the Province than in the other three ... I can say honestly to you that in no other previously or presently endemic region are so many engaged in smallpox eradication; in no other endemic region are health services, transport and communications so well developed nor the populations so willing to accept vaccination." (SE/72.9, Henderson.)

Despite the fact that the surveillance system in Sind had improved little, the total of recorded cases in 1972 rose to unprecedented levels. This event, coupled with the conference, served at last to stimulate the health authorities to undertake a more effective programme.

Following the conference, activities were reorganized. Additional surveillance teams

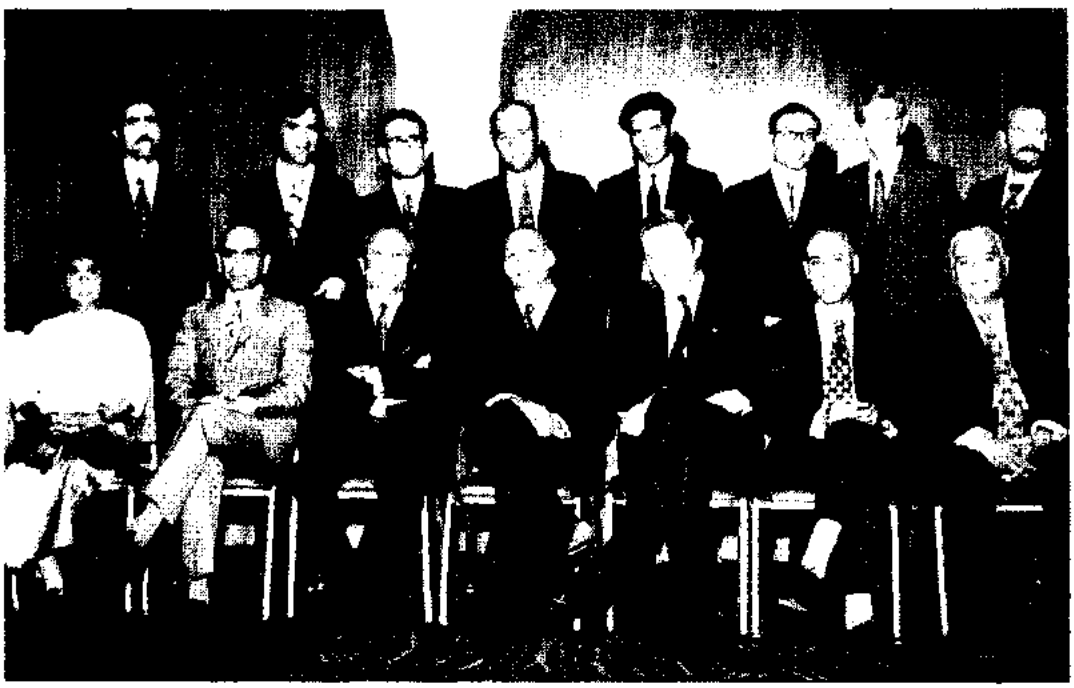

Plate 14.8. Participants in the training seminar in Karachi, Pakistan, in November 1972. *Left to right, front row:* Khin Mu Aye (WHO), A. J. Hajian (WHO), A. K. Tabibzadeh (WHO), A. W. Katpar (Pakistan), D. A. Henderson (WHO), E. Shafa (WHO), F. Jurji (Iraq); *Back row:* N. Mohammad (Afghanistan), A. M. Darmanger (Afghanistan), unidentified, M. A. Dardmal (Afghanistan), M. Salehi (Afghanistan), G. D. Suleimanov (WHO), V. V. Fedorov (WHO), unidentified.

were constituted for search and containment and soon the number of reported cases increased dramatically (Fig. 14.20), from 3661 in 1972 to 7848 in 1973. Even so, detection was greatly delayed and when outbreaks were found, containment was poorly executed. The problem was apparent from the observation that 43% of all outbreaks in 1972 and 24% in 1973 lasted more than 4 weeks (Table 14.36); 15% of all outbreaks in 1972 and 9% in 1973 had 11 or more cases (Table 14.37).

By the autumn of 1973, it was apparent that additional measures would be required. Whatever had been said about a change in strategy, district and local supervisory staff continued to be preoccupied with routine vaccination, undertaking case search and outbreak containment only with reluctance. Accordingly, in October 1973, activities were implemented that were similar to those which had been developed in India. To emphasize that the objective of the programme was to detect cases, vaccinators were redesignated "surveillance agents". Teams of 2–3 persons were scheduled to visit once a month all villages (usually 100–150) in 2–3 union council areas to detect and contain outbreaks. Activities

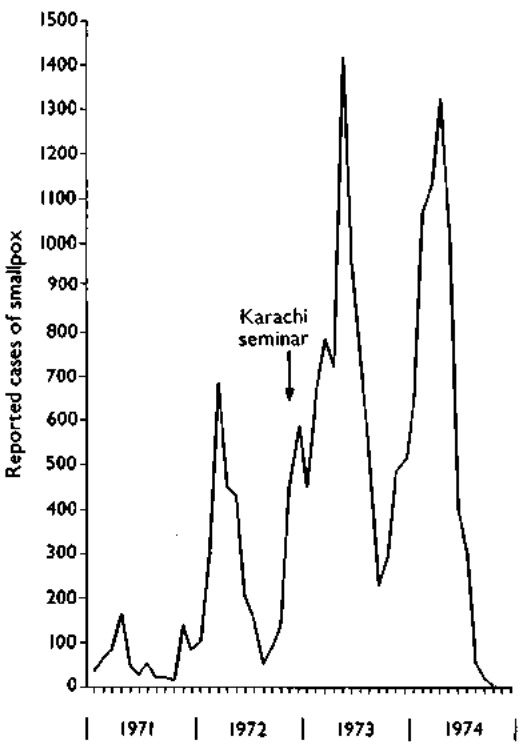

Fig. 14.20. Pakistan, Sind Province: number of reported cases of smallpox, by month, 1971–1974.

Table 14.36. Sind Province: interval between first and last cases of smallpox in outbreaks, 1972–1974

Year	Number of outbreaks	Under 1 week (%)	1–2 weeks (%)	3–4 weeks (%)	More than 4 weeks (%)
1972	727	101 (14)	189 (26)	127 (17)	310 (43)
1973	1 278	429 (34)	325 (25)	216 (17)	308 (24)
1974	1 272	671 (53)	367 (29)	191 (15)	43 (3)

Table 14.37. Sind Province: numbers of outbreaks and cases of smallpox, 1972–1974

Year	Total number of outbreaks	1 case (%)	2–10 cases (%)	11 or more cases (%)
1972	727	200 (27)	420 (58)	107 (15)
1973	1 278	451 (35)	712 (56)	115 (9)
1974	1 272	639 (50)	552 (43)	81 (7)

were supervised on the spot by a district superintendent of vaccination and a district smallpox eradication medical officer. Several provincial teams assisted in districts with the greatest problems. In Karachi, staff of the family planning and malaria control programmes participated in the search for cases. To encourage participation, a reward of 5 rupees (US$0.50) was offered to anyone finding a case. However, as a provincial surveillance officer observed, even this sytem of active search was poorly executed, the searchers devoting more time to obtaining the signatures of village leaders and teachers to prove they had been to the village than to searching for cases. The comparatively few special surveillance teams actually discovered more cases through questioning schoolteachers and persons encountered during their travel.

The results were dramatic nevertheless. Cases were discovered more promptly and were better contained. In 1974, 50% of all outbreaks consisted of only a single case and only 43 out of 1272 (3%) lasted more than 4 weeks.

During the summer of 1974, the number of cases fell steeply, from 1100 in May to 300 in June and only 55 in August. This corresponded to the customary seasonal decline in incidence observed throughout Pakistan, but with the momentum of search and containment achieved during the winter months, the few remaining outbreaks were more effectively contained. Finally, on 28 September, the last case occurred in Sanghar District, just prior to the beginning of the seasonal increase in transmission. However, programme staff remained sufficiently sceptical of the

adequacy of surveillance that months were to elapse before they expressed confidence that transmission had in fact been interrupted.

Cases and deaths in Sind for the period 1972–1974 are shown in Table 14.38. Half of all the cases were in children under 5 years of age and only 8% were in individuals aged 15 and over, a marked contrast to the situation in Baluchistan. The overall recorded case-fatality of only 9% was unusually low for the subcontinent. Data from the city of Karachi (Table 14.39) suggest that this probably reflected incomplete notification of deaths in a province in which surveillance was notably poor.

As noted before, surveillance in Karachi had been consistently better than in the rest of Sind since 1971 and the cases which occurred during 1973–1974 had resulted primarily from importations from other parts of the province. Even when standardized for age, case-fatality rates were substantially greater than for the province as a whole, almost certainly reflecting more complete documentation of deaths rather than a difference in virus strains. A similar phenomenon had been observed in Indonesia, in which case-fatality rates were far higher in the city of Jakarta than in the surrounding West Java Province.

Table 14.38. Sind Province: number of reported cases of and deaths from smallpox and case-fatality rates, by age group, 1972–1974

Age group (years)	Cases		Number of deaths	Case-fatality rate (%)
	Number	%		
<1	917	5	235	26
1–4	7 720	45	780	10
5–14	7 206	42	456	6
≥15	1 341	8	154	11
Unknown	307		21	
Total	17 491	100	1 646	9

Table 14.39. Karachi: number of reported cases of and deaths from smallpox and case-fatality rates, by age group, 1973–1974

Age group (years)	Cases		Number of deaths	Case-fatality rate (%)
	Number	%		
<1	63	11	27	43
1–4	222	38	46	21
5–14	234	40	44	19
≥15	68	11	23	34
Total	587	100	140	24

Northern areas of Pakistan—Gilgit and Azad Kashmir

In the federally administered, sparsely populated areas of Gilgit and Azad Kashmir, no special programmes were launched until 1974. Because the problems in the more populous areas of Pakistan were so formidable, neither national nor WHO staff considered it desirable to divert resources to these areas before then. It was hoped that in these northern areas, in which the population density was low, the transmission of smallpox might terminate spontaneously or be interrupted by control measures if cases were introduced. This proved to be the case. The population in Gilgit, estimated to be 450 000, lived in 5 different valleys in scattered hamlets and very small villages. A single rough road, open only 2 days a week, connected this area with the large urban centre of Rawalpindi, located in Punjab Province; as for connections by air, the single daily flight was often cancelled owing to bad weather. Between 13 000 and 100 000 vaccinations were recorded each year by hospital and dispensary staff. A reporting system was all but nonexistent. To assess the status of this area, an extensive search was conducted in the summer of 1976 but no evidence of recent cases of smallpox was discovered. Two unreported outbreaks were documented: 1 person in the eastern part of the region had developed smallpox and died in 1972, a week after returning from Karachi; and, in January 1971, 37 cases had occurred in the town of Gilgit, the largest urban centre in the region. Following the Gilgit outbreak, health staff, assisted by army personnel, had vaccinated nearly 150 000 persons. No surveys were done to document the levels of vaccinial immunity but it is doubtful that they were high.

Azad Kashmir, like Gilgit, is sparsely settled (population in 1975, 1 558 000), the people living in villages widely scattered over about 11 500 square kilometres of mostly hilly terrain. Many of the men travelled outside the area for work and, as a result, smallpox was introduced sporadically. In 1973, a special vaccination campaign was conducted by personnel of the 184 stationary health units, during which 1 381 294 persons were reported to have been vaccinated. Because of the lack of supervision or assessment of the programme, this figure was thought to be exaggerated. No information regarding cases was available before 1974,

Table 14.40. Dera Ghazi Khan, Bahawalnagar and Rahimyar Khan: results of variolation scar survey, by age group, 1976

Type of area	District	Number examined	Number variolated, by age group (years)					
			0–2	3–4	5–14	⩾15	Total	% of total examined
Riverine	Dera Ghazi Khan	9 075	0	0	4	55	59	0.7
	Rahimyar Khan	294	0	0	3	45	48	16.3
Desert	Rahimyar Khan	311	0	2	36	185	223	71.7
	Bahawalnagar	586	0	0	0	51	51	8.7

when an epidemiologist was assigned to the area. Between February and June, he documented the occurrence of 14 cases in 7 separate outbreaks, the last case occurring on 11 June 1974. No data were collected concerning the source of infection although it is assumed to have been the neighbouring province of Punjab. Extensive search in 1976 by special teams assisted by malaria control staff and local health personnel confirmed the absence of smallpox.

Variolation in Pakistan

Variolation continued to be practised in isolated areas in Pakistan throughout the duration of the programme but it was far less extensive than in Afghanistan or Ethiopia and did not significantly affect progress. As has been noted above, the last cases in Baluchistan occurred in an isolated desert area of Kalat District, but evidence of recent variolation was also observed in the southern desert of Punjab and in mountainous tribal areas bordering Afghanistan.

Variolation in Punjab was limited to the Rahimyar Khan desert near the borders with Sind and Baluchistan; this practice persisted through 1973, and one unsuccessful attempt was detected as late as 1974. A survey in 3 districts in this desert area revealed extensive variolation in the past but no evidence of it in the preceding 4 years except in Rahimyar Khan (Table 14.40).

In the tribal areas of North-west Frontier Province, variolation by traditional variolators, as in Afghanistan, had been common. An investigation was conducted in 1976 in one such area in Mohmand Agency during which the inhabitants of 31 villages were checked for the scars of variolation and the pockmarks of smallpox (Table 14.41).

More than three-quarters of the population over 10 years of age had variolation scars but surprisingly few had pockmarks. Evidence of variolation and/or pockmarks was seen only in children 3 years of age and older. This was supportive evidence that variolation had ceased, since it was usually performed when children were 1–2 years of age.

Table 14.41. Mohmand Agency: results of survey of variolation scars and pockmarks of smallpox, by age group, January 1976

Age group (years)	Number examined	With variolation scars		Number with pockmarks
		Number	%	
0–2	82	0	0	0
3–4	90	3	3	2
5–10	180	85	47	4
11–15	145	121	83	12
16–20[a]	143	102	71	14
⩾21[a]	216	163	75	19
Total	856	474	55	51

[a] Males only.

CONCLUSIONS

Following the occurrence of the last case of smallpox in Pakistan in October 1974, extensive searches were repeatedly conducted throughout the 4 provinces and 2 federally administered regions to confirm the absence of smallpox; a reward of 100 rupees, later increased to 5000 rupees, was offered to anyone reporting an outbreak. Because of the programme's earlier record of poor performance and the inadequacy of surveillance, uncertainty existed until the end of the year as to whether transmission had actually been interrupted. Only after several months of continuing search during the period of high seasonal transmission did national and international staff begin to feel reassured.

The situation in Afghanistan was entirely different. Since 1970, continuing efforts had been made to strengthen reporting and all outbreaks had been carefully investigated,

their sources traced and the outbreaks contained. Surveillance was sufficiently extensive that when cases ceased to be detected, the Afghan staff were confident within a matter of weeks that natural transmission had ceased. However, since smallpox was still widely prevalent throughout Pakistan, there was a serious risk of its being reintroduced into Afghanistan and becoming re-established there. Indeed, transmission was interrupted more than 2 years earlier in Afghanistan than in Pakistan. Importations did occur but an effective surveillance programme quickly detected and contained the outbreaks.

In Afghanistan, there were few resources and only a rudimentary health infrastructure. Nevertheless, a highly effective programme rapidly took shape once a national commitment to the programme was made. In Pakistan, the resources were extensive, immunity was already high and a sound scientific basis for a programme had been elaborated. That Pakistan required so much longer to interrupt transmission reflects the difficulties of endeavouring to replace entrenched traditional doctrine—in this case, "100% vaccination"—with an alternative strategy that called for the detection and containment of outbreaks. Progress was unquestionably impeded by the attitude of some WHO advisers who, for so long, were not completely persuaded that this approach was correct. The delegation of authority and responsibility for health policy and programmes from national to provincial level further compounded the problem. Although national authorities attended the World Health Assembly, discussed global health policies and made commitments on behalf of Pakistan, provincial authorities bore the responsibility for deciding policy and priorities within their own jurisdictions. Some supported an eradication programme while others exhibited little interest. National authorities could do no more than exhort and cajole. In consequence, a successful effort in North-west Frontier Province was jeopardized by the sudden collapse of the programme in Punjab, and both programmes were compromised by repeated importations of smallpox from Sind and Baluchistan, neither of which exhibited interest in smallpox eradication until late in the programme.

The question arises, in respect of Afghanistan, whether surveillance–containment measures alone might have succeeded, in view of the fact that transmission was interrupted so rapidly once these measures had been taken. Given the extent of variolation, it seems doubtful, in retrospect, that the staff could have dispensed with mass vaccination and the accompanying programme designed to educate village leaders and the villagers themselves about the dangers of variolation and the advantages of vaccination.

In 1968, the attainment of eradication in Afghanistan had been considered to represent the Intensified Programme's most difficult challenge. With the interruption of transmission there, senior WHO staff speculated anew as to which country or area might constitute the insuperable obstacle to global eradication. A few thought that it might be Ethiopia. Most, however, conjectured that it would be the populous country of India, which was generally believed to be the original home of smallpox and in which, perhaps, unique factors of climate, crowding, etc., permitted transmission to persist as in the case of cholera. In the next chapter we shall turn to the programme in India.

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CHAPTER 15

INDIA AND THE HIMALAYAN AREA

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INTRODUCTION

The Indian subcontinent has long been regarded as the probable place where smallpox originated—its traditional endemic home. It was a disease described in early Indian writings and enshrined both in Hindu religious belief and throughout the country in temples to the smallpox goddess. Variola major, with a case-fatality rate of 20% or higher, was the only variety of smallpox found in India and, as recently as the 1950s, it is estimated to have killed more than a million persons annually. Many held the view that because of population density, or for other ill-defined socio-cultural or epidemiological

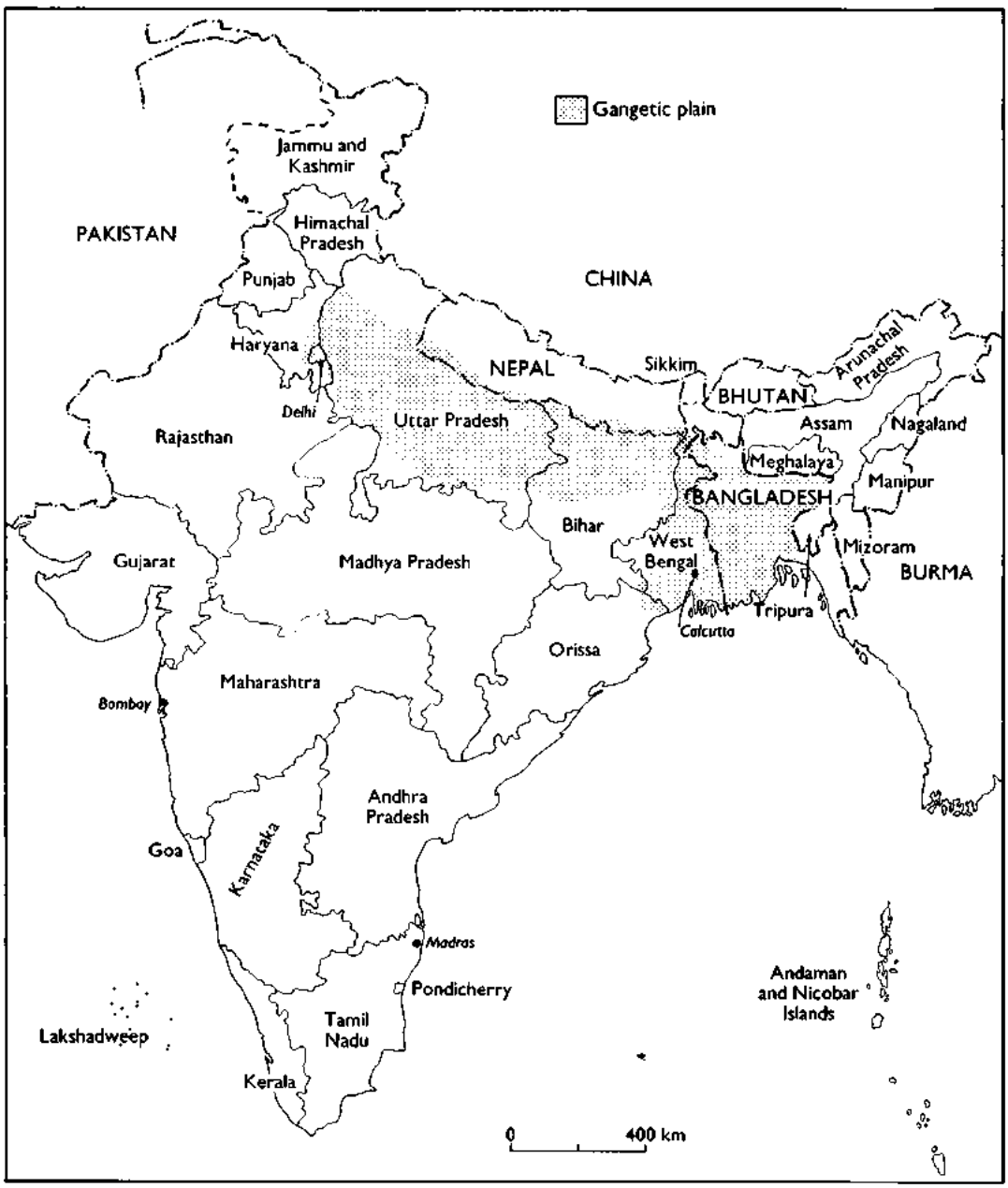

Fig. 15.1. Bhutan, the states and union territories of India, and Nepal. Many of the most densely populated areas in the region are in the Gangetic plain. In India, Karnataka was known as Mysore until 1973; Arunachal Pradesh was the North East Frontier Agency until 1971; and Sikkim became a state in 1975. Bangladesh was East Pakistan until 1971.

reasons, the eradication of smallpox in India would ultimately prove impossible. This belief had its roots in the behaviour of cholera, which for centuries had been confined to the riverine areas of the Indian subcontinent. In the 1830s, cholera spread across the world in the first of seven global pandemics, only to disappear over time, except from the Ganges river plain (Fig. 15.1). Although cholera was a bacterial disease with wholly different epidemiological characteristics, many believed that there were unique, yet unrecognized features of this area which would doom a smallpox eradication effort as certainly as an effort to eliminate cholera.

There were other reasons for pessimism. In area, India was the world's seventh largest country but second only to China in size of population. Of the 1100 million people living in areas which had endemic smallpox in 1967,

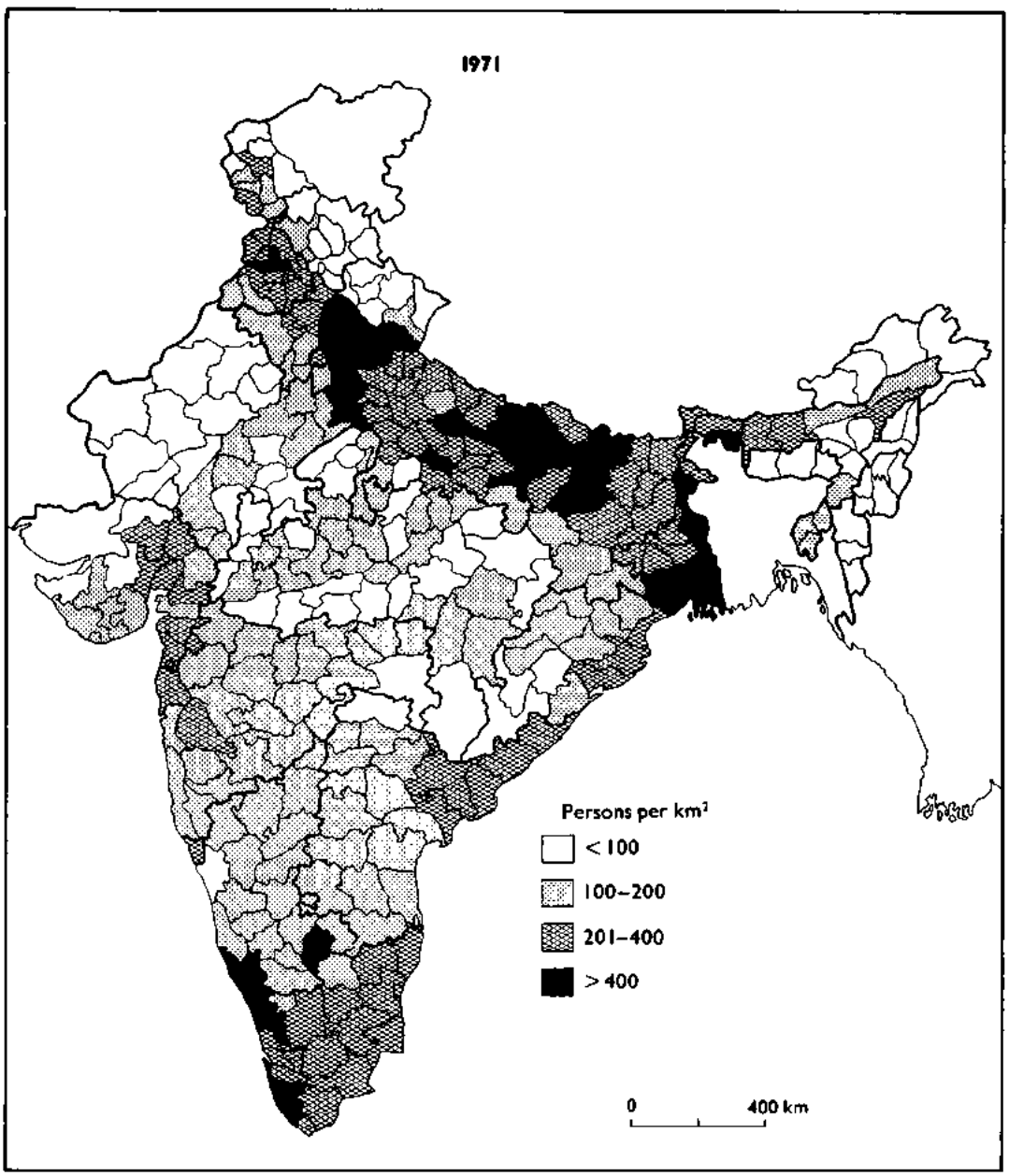

Fig. 15.2. India: population density, by district, 1971.

513 million (47%) lived in India. The most densely populated zone was the Ganges river plain in the north (Fig. 15.2), some 2400 kilometres long and 240–320 kilometres wide. Sharing borders with India and epidemiologically related to it were the 2 small Himalayan mountain kingdoms of Nepal (population 10.8 million) and Bhutan (population, 987 000), and the Indian protectorate of Sikkim (population, 196 000). (Sikkim became an Indian state in 1975.)

A smallpox eradication campaign had begun in India in 1962 (Fig. 15.3) but, despite an intensive and costly effort, smallpox was still widely prevalent in 1967 and substantially underreported throughout the country. A pilot smallpox control programme had been launched in Nepal in 1962, but cases continued to be reported from the only 3 districts which reported at all. Little was known in 1967 about the situation in Bhutan and Sikkim.

In 1967, the meagre resources available to WHO precluded the provision of meaningful support to all endemic countries in Asia. A programme was already established in India, although functioning poorly, and India at that time requested international assistance only to permit the acquisition of equipment for vaccine production. Thus, WHO's assistance in Asia was directed to the less populous endemic countries—Afghanistan, Indonesia, Nepal and Pakistan (which then included East Pakistan, later to become Bangladesh). It was hoped that successful programmes in these countries would eventually permit the release of significant resources in support of the Indian national programme if required. A joint India–WHO team assessed the Indian programme in 1967 and, subsequently, WHO staff from Headquarters and the Regional Office for South-East Asia in New Delhi held frequent meetings with Indian government staff. Until 1970, however, progress was slow. That year, a WHO–India agreement was signed which provided for WHO support for field activities. During the following 3 years considerable progress was made in the southern and western states but little in the northern, densely populated Ganges river plain. Meanwhile, country after country in Africa, South America, and Asia succeeded in interrupting smallpox transmission. By June 1973, only 5 endemic countries remained, of which 4 were adjoining countries in Asia (Bangladesh, India, Nepal and Pakistan) and the fifth was in Africa (Ethiopia).

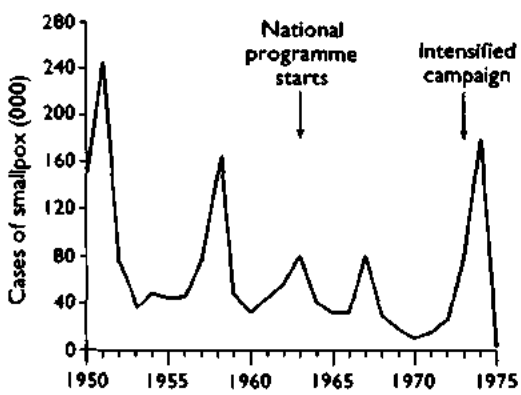

Fig. 15.3. India: number of reported cases of smallpox, by year, 1950–1975.

In June 1973, Indian and WHO staff decided on an ambitious campaign to involve more than 100 000 local health staff throughout India in a village-by-village search for cases. Such searches would be completed in 7–10 days and would be undertaken monthly in heavily infected areas and less often in areas in which few or no cases were being reported. Outbreaks, when found, would be contained by local health staff assisted by state and district surveillance teams. With this strategy, it was hoped that transmission might be sharply curtailed by January 1974 and perhaps interrupted as early as June 1974. The problems proved far more formidable than had been foreseen. Although the original optimistic target was not met, transmission was interrupted in May 1975, less than 2 years after the special programme had begun—a considerable achievement in so vast a country.

In sheer magnitude and scope, in innovation and adaptation to adversity, in dedication and enthusiasm, in the degree of international cooperation and understanding, the Indian programme from September 1973 onwards was one of the finest endeavours of the global campaign. It is impossible to do full justice to this vast programme in a single chapter. Fortunately, a number of publications describe the overall programme, focusing primarily on its concluding phase. Two books, *The Eradication of Smallpox from India* (Basu et al., 1979) and *The Management of Smallpox Eradication in India* (Brilliant, 1985), are particularly valuable. Special issues of the *Indian journal of public health* (January–March 1978) and *The journal of communicable diseases* (August 1975) also provide important information.

This chapter includes an account of the closely related and ultimately well-executed Nepalese programme, of which there is no published description. It concludes with such information as is available regarding activities in Bhutan and Sikkim, which experienced only infrequent importations after 1966.

INDIA

Background

India's immense size and vast population, of whom more than 80% lived in rural areas, was but part of the challenge. In India, as well as in East and West Pakistan, there was an extraordinary movement of population from place to place for purposes of business and attendance at marriages and funerals. Numerous religious pilgrimages and gatherings attracted huge crowds, sometimes amounting to millions of people. Uncountable hundreds of thousands travelled throughout the country on 10 800 daily trains. The state transport system, including buses and other motor vehicles, alone carried some 10 million passengers (about 2% of the population) each day. Reflecting the extent of internal migration, the 1961 census showed that a third of the population was enumerated outside their places of birth that year; during succeeding years, mobility substantially increased. This was important in smallpox transmission. Often, persons who were exposed to or became ill with smallpox would journey long distances to return to their home villages, disseminating smallpox when they arrived and sometimes in the course of the journey.

Also unique to the Indian setting was a belief among Hindus that attributed smallpox to the wrath of a goddess, called Sītalā (Shitala) mata although known by a number of different names among India's 15 major language groups and 250 regional dialects. It was not surprising that a deity was associated with smallpox, considering the antiquity of the disease and the large numbers of people it afflicted, of whom 1 in 5 died. Its severity was illustrated by the fact that as late as the mid-1800s, 13% of all recorded deaths in Calcutta were due to smallpox, and 75% of blindness in India at that time was attributed to the disease (Rogers, 1944). Some persons resisted vaccination, fearing that it would anger the goddess. Religious ceremonies in her honour were common at specially dedicated temples as well as in people's homes.

Finally, there were the complexities of the administrative structure. India, a parliamentary democracy, was divided into 21 states and 9 union territories. (In 1975, Sikkim became the 22nd state.) These were further subdivided into 393 districts and 5247 community development blocks (Table 15.1). Of the 575 721 villages enumerated in the census of 1971, approximately 319 000 had a population of less than 500; only 6333 had a population of more than 5000. There were only 4 cities with more than 2 million inhabitants: Calcutta (7 million), Bombay (6 million), Delhi (3.6 million), and Madras (3 million).

At the national level, responsibility for health programmes was shared by the Minister of Health, a political figure; the Secretary of Health, a non-technical administrative executive officer; and a technical Director-General of Health Services, who implemented health programmes. Substantive decisions required the collaborative understanding of all three. In each state the administrative structure replicated the national one. Although there was some variation in the type of organization from state to state, there were district health units in most, directed by a chief medical officer of health (or civil surgeon). In large states, several districts were grouped in divisions and, for each, there was a divisional medical officer. Districts were divided into basic health units termed primary health centres (corresponding usually to community development blocks), which attended to the health needs of 80 000–150 000 people living in 150–350 villages.

Smallpox in India before 1962

Vaccination had first been performed in India in 1802 and an organized vaccination programme was begun in Bombay in 1827 (Rogers, 1944). By 1868, some type of vaccination programme had been established in all provinces, although little was done in most of the 560 independent princely states, in which about a third of the population resided. With increasing numbers of vaccinations, the numbers of registered deaths from smallpox declined between 1878 and 1937, despite a progressively improving system for the regis-

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Plate 15.1. The goddess of smallpox has long been worshipped throughout the Indian subcontinent. She is usually portrayed as a woman riding on an ass, carrying a broom in one hand and a waterpot in her other arm. In northern India, she was known as Śītalā mata, śītalā meaning the cool one, and mata meaning mother. Though worshipped primarily by Hindus and Jains, in Nepal she was incorporated in the Buddhist pantheon as Ajima, the mother of Gautama Buddha. Offerings were made at temples dedicated to her and to images in the home; annual festivals were held on her feast day. Beliefs and practices differed from place to place and the goddess was variously considered to have powers to prevent or cure the disease as well as to inflict it.

Table 15.1. India: political divisions, area and population distribution, 1971[a]

Region and state or union territory[b]	Area (km^2)	Population (1971)	Population density/km^2	Number of			
				Districts	Blocks	Towns	Villages
South:							
Andaman and Nicobar Islands[c]	8 293	115 133	14	2	5	1	390
Andhra Pradesh	276 814	43 502 708	157	21	324	207	27 221
Dadra and Nagar Haveli[c]	491	74 170	151	1	2	—	72
Goa, Daman and Diu[c]	3 813	857 771	225	3	12	13	409
Kerala	38 864	21 347 375	549	11	144	88	1 268
Lakshadweep[c]	32	31 810	994	1	4	—	10
Maharashtra	307 762	50 412 235	164	26	426	257	35 778
Mysore[d]	191 773	29 299 014	153	19	268	230	26 826
Orissa	155 782	21 944 615	141	13	314	78	46 992
Pondicherry[c]	480	471 707	983	4	4	5	333
Tamil Nadu	130 069	41 199 168	317	15	374	241	15 735
East:							
Assam	78 523	14 625 152	186	10	130	69	22 224
Manipur	22 356	1 072 753	48	6	26	8	1 949
Meghalaya	22 489	1 011 699	45	3	24	3	4 583
Mizoram[c]	21 087	332 390	16	3	20	2	[f]
Nagaland	16 527	516 449	31	7	21	3	960
North East Frontier Agency[c,e]	83 578	467 511	6	5	43	4	2 973
Tripura	10 477	1 556 342	149	3	17	6	4 727
West:							
Chandigarh[c]	114	257 251	2 257	1	1	1	26
Delhi[c]	1 485	4 065 698	2 738	2	5	1	243
Gujarat	195 984	26 697 475	136	19	250	200	18 275
Haryana	44 222	10 036 808	227	11	87	65	6 731
Himachal Pradesh	55 673	3 460 434	62	12	69	35	16 916
Jammu and Kashmir	222 236	4 616 632	21	10	74	43	6 503
Punjab	50 362	13 551 060	269	12	117	106	12 188
Rajasthan	342 214	25 765 806	75	26	232	151	33 305
Central:							
Bihar	173 876	56 353 369	324	31	587	161	67 566
Madhya Pradesh	442 841	41 654 119	94	45	457	233	70 883
Uttar Pradesh	294 413	88 341 144	300	55	875	293	112 561
West Bengal	87 853	44 312 011	504	16	335	137	38 074
Total	3 280 483	547 949 809	167	393	5 247	2 641	575 721

[a] From Basu et al. (1979), including the population estimates. United Nations (1985) data show a total population of 564 207 000 for India as a whole in 1971.

[b] The regional divisions (South, East, West and Central) shown in this and other tables were designated by the staff of the Intensified Smallpox Eradication Programme on the basis of the epidemiological characteristics of smallpox and the status of the programme in 1972. Reference is made to them in describing the progress of the programme. Sikkim, which became a state of India in 1975, is not listed.

[c] Union territories.

[d] Became the state of Karnataka late in 1973.

[e] Became the union territory of Arunachal Pradesh in 1972.

[f] Included in Assam.

Table 15.2. India: population, number of recorded deaths from smallpox, average annual number of vaccinations, and percentage of population vaccinated annually, 1878–1937[a] (British India) and 1962–1971

Years	Population	Total number of deaths	Average annual number of vaccinations	Percentage of population vaccinated annually
1878–1887	190 000 000	1 460 890	4 750 000	2.5
1888–1897	206 000 000	961 424	6 750 000	3.3
1898–1907	222 000 000	832 165	8 750 000	3.9
1908–1917	234 000 000	851 999	9 500 000	4.0
1918–1927	240 000 000	832 477	14 500 000	6.0
1928–1937	263 000 000	763 279	19 100 000	7.3
1962–1971	513 000 000[b]	113 372	91 940 000	18.0

[a] From Rogers (1944).

[b] United Nations (1985) estimate for 1967.

tration of deaths and a growing population (Table 15.2). Data comparable to those provided by Rogers could not be obtained for the period 1937–1961, but data for 1962–1971 are available—1962 being the year in which India commenced a special national smallpox eradication programme (see below). It is not known how complete the registration of deaths may have been at different times. However, studies conducted during the early 1970s showed that even then, the number of reported cases of, and presumably deaths from, smallpox represented less than 5% of the cases and deaths that had actually occurred.

Vaccination programmes were gradually extended throughout most of the country and, following India's independence in 1947,

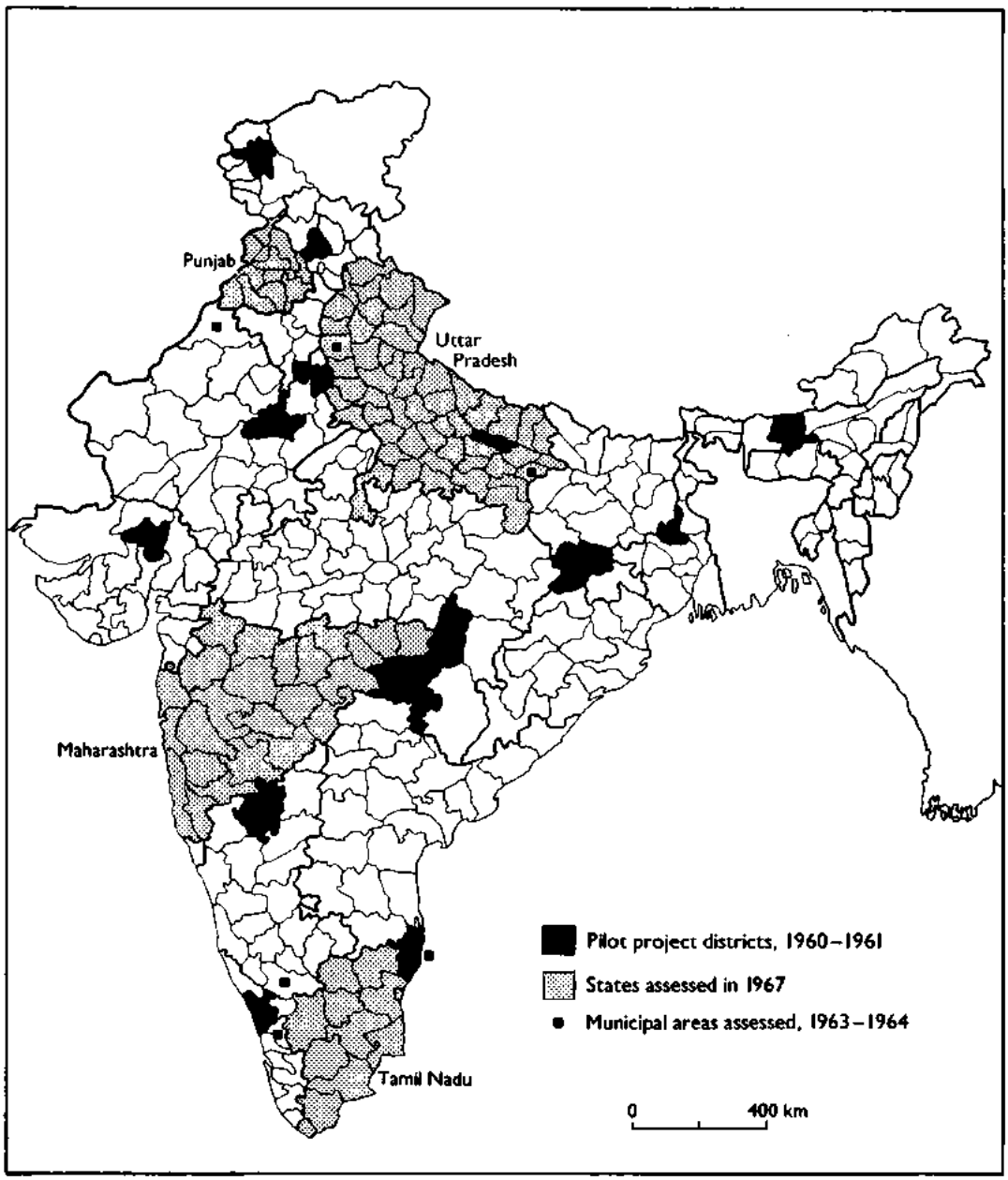


Fig. 15.4. India: pilot project districts for the National Smallpox Eradication Programme (NSEP), 1960–1961; state programmes assessed in 1967; and municipal areas assessed, 1963–1964.

to the remaining princely states. Thermolabile liquid vaccine was the only vaccine available and many of the vaccinations performed must have been unsuccessful. This vaccine was produced in 14 laboratories in 11 different states. As in Pakistan, vaccinators who were recruited and hired by the local administrative organization and termed "local body vaccinators" performed the vaccinations. The programme of vaccination provided only partial control of smallpox, but because vaccination was widely available and variolation was forbidden by law, the latter practice ceased and, by the late 1950s, was no longer a problem in India.

India's National Smallpox Eradication Programme, 1962

In June 1959, one month after the decision of the Twelfth World Health Assembly to undertake a global eradication programme, an Expert Committee of the Indian Council of Medical Research recommended that a National Smallpox Eradication Programme should be established. The vaccination campaign that resulted was of heroic dimensions and, although failing in its goal to eradicate smallpox, it served to extend vaccination to all but the most isolated villages and created an army of workers and a momentum which provided a foundation for the subsequently successful eradication effort.

Pilot projects were first developed in one district per state to work out methodology and to develop estimates of costs and personnel requirements (Fig. 15.4). The projects began in 1960 and concluded in March 1961 (India, Ministry of Health and Family Planning, 1966).

The essence of the strategy called for a specially recruited team to move systematically from house to house and from village to village throughout a district in an effort to vaccinate or revaccinate not less than 80% of the population. With this proportion vaccinated, it was expected that a sufficient number of persons would be immune so that smallpox transmission would terminate spontaneously. The vaccination team was preceded by enumerators, who listed in a large multi-page register the name of each person along with his or her address, age, sex and previous history of vaccination or of smallpox. One register was compiled for each village or defined area in a city and was intended to be used during the subsequent 20 years. After enumeration had been completed, the register was given to the vaccination team, which then endeavoured to vaccinate those who were listed. The register was next given to an inspector, who was to check each vaccinee to ensure that vaccination had been successful. Subsequently, local health unit vaccinators (1 for every 50 000–70 000 persons) were assigned responsibility to vaccinate those missed in the mass campaign ("mopping-up vaccination"), to maintain the registers, to revaccinate everyone every 5 years and to vaccinate contacts when cases were discovered. Performance in the pilot projects was poor. In a target population of 23 million, only 12 million (52%) were vaccinated. No evaluation of the programme was conducted nor was smallpox incidence monitored. Nevertheless, as happens only too frequently, the pilot projects were followed almost immediately by the introduction of a national programme.

The USSR offered freeze-dried vaccine, which was largely but not entirely intended to replace the thermolabile liquid vaccine; the United States Agency for International Development made a grant of rupees equivalent to US$2 million; and UNICEF pledged equipment for vaccine production. Eventually, the USSR provided 650 million doses of vaccine and the USA, between 1961 and 1967, contributed the rupee equivalent of US$23 million, which had been generated by the sale of foodstuffs provided to India (termed Public Law 480 funds).

Since health programmes in India are constitutionally a state responsibility, the principal administrative direction of the smallpox eradication programme was delegated to the states. Only 2 professional staff provided coordination at the national level. However, because smallpox was considered a national priority, the programme was "centrally sponsored"; the states were reimbursed by the central government for all non-recurring expenditures and for 75% of recurring costs.

The government created 152 units, each of which was expected to vaccinate about 3 million persons in an "attack phase" lasting 2–3 years. Each unit consisted of a supervising officer (usually a physician), a paramedical assistant, 60 vaccinators, 12 inspectors, 12 enumerators and 2 health educators. Each unit was assigned 3 vehicles. In all, more than 13 000 persons were employed, most of whom

Recommendations for Primary Vaccination in Early Childhood, 1963

The programme's recommendations for primary vaccination were taken from a publication of the British Ministry of Health and distributed in a circular to all administrative staff in 1963. It stated that primary vaccination "should be carried out some time before the age of two years, preferably during the second year" and listed as specific contraindications: "failure to thrive, exposure to infectious disease, septic skin conditions, infantile eczema and other allergic conditions, hypogammaglobulinaemia and corticosteroid treatment" (India, Ministry of Health and Family Planning, 1966). Although perhaps appropriate for the United Kingdom, where smallpox cases were only occasionally imported, the recommendations were inappropriate for India, where many children were exposed to smallpox from birth, where the risks associated with vaccinating most of those with the listed contraindications were much less than the risk of death due to smallpox, and where most vaccinations were performed by scarcely literate vaccinators who could not be expected to recognize many of the conditions noted. Indeed, if all the contraindications had been carefully observed in India, few children would have been vaccinated. Sensibly, the recommendations were largely ignored by most vaccinators, although some did not vaccinate children who were ill with fever or had skin infections. Throughout India, 3 months of age was generally respected as the lower age limit for vaccination. By 1970, a more realistic and appropriate policy had evolved. It called for vaccination from the time of birth and recognized no contraindications except one: vaccinators were instructed not to vaccinate seriously ill persons who might be expected to die over the succeeding day or two and whose death might thus erroneously be attributed to vaccination.

were newly hired and trained. The programmes were launched in 1962 and 1963.

Between 1962 and 1966, 440 million vaccinations were reported to have been performed. It was an impressive number but it did not signify that this many persons had been rendered immune. The first indication of difficulties was observed in New Delhi in the winter of 1963 (Gelfand, 1966). Between December 1962 and May 1963, 346 cases of smallpox occurred in an area in which the number of vaccinations performed was equivalent to more than 80% of the population. Sample surveys conducted in 18 representative areas revealed that, in fact, vaccinations had been given to only 63% of the population and that, of these, 86% had been successful. It was therefore concluded that only 54% of the population had been successfully vaccinated. This discrepancy between the number of vaccinations reported and the number of people actually rendered immune was attributed to a falsification of records and the repeated vaccination of readily accessible groups, particularly schoolchildren. The government was disturbed by these findings and asked India's National Institute of Communicable Diseases to undertake similar surveys in other states. Five were subsequently conducted in districts which reported that the number of vaccinations performed was equivalent to 80% or more of the population. In operational terms, this meant that the mass campaign "attack phase" had been completed or was about to be completed and the "maintenance phase" was due to begin; during the latter phase the established health services would assume the responsibility for sustaining levels of vaccinial immunity and for controlling outbreaks.

The findings of the National Institute's teams were not encouraging (Gelfand, 1966). The family registers—printed sheets sewn together in a large book—were supposed to include the name of each individual in a defined area and to provide a permanent record of vaccination status. Field assessment showed that many registers had already been lost or were so worn as to be unusable; many names had been omitted; and the clerical task of keeping the registers up to date was overwhelming. It was found, for example, that some individuals who had died as long as a year before were recorded as having just been successfully revaccinated. However in-

Table 15.3. India: number of reported cases of smallpox, by state or union territory, 1962–1975

State or union territory	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975
South[a]														
Andhra Pradesh	3 065	3 519	3 256	2 339	981	8 618	7 951	1 893	358	214	405	1 295	281	0
Dadra and Nagar Haveli	0	0	0	0	0	18	2	0	0	0	0	1	0	0
Goa, Daman and Diu	16	4	0	180	127	45	18	12	1	0	0	0	0	0
Karnataka	1 310	2 844	787	1 879	1 708	1 770	981	178	126	223	1 299	6	11	0
Kerala	925	1 021	62	157	517	152	2	9	31	0	0	0	4	0
Lakshadweep	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Maharashtra	6 820	15 323	6 567	7 484	8 092	27 961	3 173	1 411	174	160	215	158	448	0
Orissa	1 175	4 185	906	1 611	404	3 806	3 200	1 247	105	16	5	1 276	2 170	6
Pondicherry	40	60	53	102	1	0	0	0	0	0	0	0	0	0
Tamil Nadu	8 588	8 901	5 545	3 377	789	263	150	6	0	7	1	3	15	0
East														
Arunachal Pradesh	0	0	0	0	82	27	132	118	0	0	4	2	2	0
Assam	358	250	177	183	601	458	507	640	77	35	8	458	6 243	88
Manipur	0	18	0	6	82	33	4	0	0	0	0	13	11	0
Meghalaya	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	0	0	0	30	498	61
Mizoram	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	0	0	0	1	0	0
Nagaland	..	..	0	0	31	28	0	0	0	0	0	45	45	0
Tripura	13	2	0	104	0	109	341	0	0	0	6	9	0	9
West														
Chandigarh	*c*	*c*	*c*	*c*	..	12	0	0	9	0	0	0	0	0
Delhi	175	484	92	296	475	472	70	28	96	318	149	168	142	0
Gujarat	1 327	609	79	310	1 170	3 403	7 654	6 284	2 492	238	39	9	5	16
Haryana	*c*	*c*	*c*	*c*	149	4 809	633	683	2 161	2 635	1 532	188	71	0
Himachal Pradesh	11	101	2	21	24	44	2	0	1	11	0	2	7	0
Jammu and Kashmir	35	33	9	7	0	40	1	7	0	11	272	941	760	0
Punjab	4 848	1 727	319	380	859	1 393	76	228	234	101	139	65	53	0
Rajasthan	3 900	3 370	1 938	1 652	1 555	4 506	1 923	1 439	4 097	4 827	1 970	877	61	0
Central														
Bihar	378	4 760	8 484	5 398	6 590	11 873	3 873	2 069	403	1 307	4 153	24 237	126 872	839
Madhya Pradesh	9 015	6 091	2 118	1 860	2 557	1 965	838	852	1 036	1 008	2 057	5 400	2 251	0
Uttar Pradesh	11 828	17 704	6 056	4 431	3 914	11 651	2 195	899	998	4 862	10 400	34 444	36 959	293
West Bengal	1 768	12 417	3 815	1 624	1 990	1 446	1 453	1 275	374	217	4 753	18 486	11 094	124
Total	55 595	83 423	40 265	33 402	32 616	84 902	35 179	19 281	12 773	16 190	27 407	88 114	188 003	1 436

[a] No cases were reported during this period in the union territory of Andaman and Nicobar Islands.
[b] Part of Assam.
[c] Part of Punjab.

effective the family registers may have been, their use continued in many areas until the late 1960s.

The proportion of the population found to have been successfully vaccinated was less than the reported 80% in all districts, ranging from 54% to 73%. Substantially lower levels of vaccination coverage were found in urban districts than in rural areas. Although the numbers reported to have been vaccinated were probably somewhat inflated, the more basic problem was similar to that observed in New Delhi: the most accessible individuals—schoolchildren, for example—were being vaccinated as often as every 6 months, while pre-school children and persons in the lowest socio-economic groups, among whom smallpox was most prevalent, were not being vaccinated at all.

In areas which had entered the maintenance phase of the programme, the National Institute's teams evaluated performance by examining children aged 3–12 months for the presence of a vaccination scar. After the mass campaign, all children on reaching 3 months of age were supposed to be vaccinated by staff assigned to the local primary health centre. In one district, 88% of children 3–12 months old had vaccination scars, but in the remaining districts the corresponding proportions were, respectively, 2%, 9%, 23% and 38%. The National Institute's teams investigated reported cases of smallpox in the maintenance phase areas and in each district they found many other cases which had not been detected.

In view of the fact that the districts evaluated were among the few which had reported that they had achieved the target of 80% coverage, it was apparent that the programme had fallen far short of expectations. An internal document issued by the United States Agency for International Development in November 1964, justifying the programme's continued use of United States rupee funds, stated prophetically: "Eradication of smallpox in India ... is at least 10 years hence ..."

Despite the extensive vaccination programmes, 30 000–40 000 cases of smallpox were reported each year during 1964–1966 (Table 15.3). Because millions had been rendered immune through vaccination, a decrease in the true incidence of the disease is assumed to have occurred, although such a decrease might have been masked by a more complete notification of cases. However, no specific measures had been taken to improve the reporting system and little is known about its efficacy at this time beyond the recognition that only a small proportion of cases was officially recorded.

Serious deficiencies extended throughout the reporting network at each level responsible for data collection and transmission. In villages, cases of smallpox, as well as of plague and cholera, were supposed to be reported to the primary health centre by the village headman in most states or, in some, by the village watchman (chowkidar)—a poorly paid, sometimes illiterate employee of the village council. Some villages submitted reports but many did not. Health workers, assigned to primary health centres, paid little attention to the reporting of smallpox.

An additional problem was that villagers sometimes deliberately hid cases to avoid vaccination, to which they objected for religious reasons or because they feared the painful, infected lesions which so often resulted from the use of the rotary lancet. Some persons who had contracted the disease concealed themselves to avoid being taken forcibly to congested and understaffed hospitals. The cases that came to the attention of primary health centre personnel and district officials were frequently not reported by them to higher authorities because they were afraid of being punished by their supervisors. Many supervisory staff acted on the premise that the occurrence of cases in an area was prima facie evidence that the health staff had done an inadequate job of vaccinating the population and so deserved punishment.

At that time, the Central Bureau for Health Intelligence, the national statistical office, simply recorded data, showing little interest in whether the districts and states reported at all. Even the simple task of recording data was confounded by a system, unique to India, which required each district to report each week the number of cases detected according to the week of onset of the cases. This differed from the practice in other countries, in which a weekly report was compiled giving the number of cases of smallpox *detected* that week, irrespective of the date of onset. Thus, instead of receiving and recording one number for each of India's 393 districts, the Central Bureau received new reports of cases for each district extending back weeks or even months. All numbers were entered in a great ledger, past numbers corrected and new

Vaccination Using the Rotary Lancet

Until the bifurcated needle began to be used in 1970, vaccination was an elaborate and time-consuming ritual. Each vaccinator had a helper who carried a vaccination bag, and the pair proceeded from house to house to identify individuals to be vaccinated. When a candidate was found, the helper unpacked the bag and the following routine, prescribed by the Directorate of Health Services, was followed (India, Ministry of Health and Family Planning, 1966):

1. Check your kit bag to make sure that all the articles are there.
2. Perform vaccinations in a shady place to prevent exposure of the lymph to the sun.
3. Before vaccinating a person, wash your hands thoroughly with plain soap and water.
4. Sterilize both the scoop end and the toothed end of the rotary lancet in water brought to the boil beforehand and kept boiling. Hold the middle of the lancet with your thumb and index finger and dip the two ends in boiling water alternately for a minute each. If quick work is required, hold the two ends of the rotary lancet alternately over a naked flame. After sterilizing the lancet, keep it on a special wooden stand, taking care to see that the two sterilized ends do not come into contact with any other object.
5. Scrub the site chosen for vaccination thoroughly with plain soap and water. Wipe it dry with a sterile swab.
6. Take the vaccine tube from the ice container, unscrew its cap, take the lymph on the scoop end of the rotary lancet, recover the tube and put it aside on a special holder. Place the lymph on the required number of spots, on the outer surface of the middle third of the left upper arm for primary vaccinations, and on the front surface of the left forearm for revaccinations. Place the toothed end of the lancet on the skin through the drop of lymph. Rotate the lancet with gentle and even pressure so as to produce a light circular cut without drawing blood. After making the insertion, rub in the lymph into the scarified area with the scoop end of the lancet. Detain the person for 15 minutes so that the lymph may have time to get absorbed into the skin.

After one or several vaccinations had been performed at a house, the bag was repacked by the helper, and the vaccinator and helper proceeded to the next house.

Vaccinators who failed to permit the lancet to cool sufficiently or who were were too vigorous in pressing it into the skin inflicted painful lesions. Because the lancets were often contaminated, the vaccination lesions frequently became septic. The scars which remained sometimes resulted from the growth of vaccinia virus but sometimes were caused by bacterial infection alone. Not surprisingly, many vaccinators were offered money *not* to vaccinate.

Given the routine and the need to record the name of each vaccinee in a large register, it was unusual for a vaccinator to perform more than 25 vaccinations a day. When the bifurcated needle became available, the procedure was greatly simplified and both the special bags and the helpers gradually disappeared. However, the pace of vaccination, by then well ingrained, did not substantially increase.

totals compiled. Similar procedures were followed by district and state statistical offices. However, many of these offices did not forward reports of cases which had occurred several weeks or months previously, considering them not to be of current interest.

The National Smallpox Eradication Programme Advisory Committee held a meeting in November 1965 to decide what should be done when, in March 1966, the attack phase—the mass vaccination campaign—was scheduled to be completed and the programme throughout the country would enter its maintenance phase (India, Ministry of Health and Family Planning, 1966). The Director of the National Smallpox Eradication Programme, Dr K. M. Lal, expressed optimism that there would be a "further steep fall" in incidence in 1966–1967 but was concerned about the large number of persons who still remained unvaccinated. Because

independent assessments had shown that equating the numbers of recorded vaccinations with the numbers of persons successfully vaccinated was erroneous, it had been decided that a target of 100% vaccination coverage was necessary (a strategy endorsed by a WHO Expert Committee on Smallpox (1964) at Dr Lal's suggestion). Dr Lal doubted that a satisfactory maintenance vaccination programme could be conducted by the existing primary health centre staff, malaria workers, midwives and others. The 1963–1964 assessment had shown this. He favoured a plan which had been suggested to and approved by the Advisory Committee in 1963, whereby 1 smallpox vaccinator would be provided for every 10 000–15 000 persons in rural areas and for every 20 000 persons in urban areas. Such a scheme would be costly and, by any standard, would involve a generous deployment of manpower. Assuming that a vaccinator worked 200 days a year, he could theoretically vaccinate the entire population in a rural area during the space of a year by performing as few as 50–75 vaccinations a day.

Dr Lal and many members of the Advisory Committee were reluctant to end the attack phase with its mass vaccination units until cases had ceased to occur in a district. Various members proposed intervals of up to 3 years as the desirable time for an area to be smallpox-free before it entered the maintenance phase and vaccination was turned over to basic health staff or local body vaccinators. A special subcommittee was appointed to explore the question further. However, budgetary considerations intruded. The government was forced to decrease expenditure, and the attack phase programme, with its 152 mass vaccination units, was terminated. Special vaccinators for smallpox continued their work in most areas, but in a few, a handful of poorly trained and poorly supervised basic health workers were expected to add vaccination to other tasks.

Meanwhile, vaccine production institutes at Patwadangar, Belgaum, Guindy (Madras) and Hyderabad struggled unsuccessfully to produce the large quantities of freeze-dried vaccine required. By 1966–1967, they were producing only 1.4 million vials (enough to vaccinate about 20 million people). The USSR continued to provide approximately 500 000 vials each month, but even this was not enough. Emergency requests to other governments were regularly channelled through WHO, and several million additional doses were received from the Netherlands, Switzerland and the United Kingdom, but none of these sources could supply substantial quantities since none had laboratories equipped for the large-scale production required. Accordingly, the thermolabile, questionably potent, liquid vaccine continued to be used in a number of states since it was felt that unsatisfactory vaccine was better than no vaccine at all.

Table 15.4. India: numbers of reported vaccinations, percentages relative to population, and numbers of reported cases of and deaths from smallpox, 1962–1976

Year	Primary vaccinations		Total vaccinations		Reported number of cases of smallpox	Reported number of deaths from smallpox
	Number	% relative to population[a]	Number	% relative to population[a]		
1962	3 520 000	0.8	32 350 000	7.2	55 595	15 048
1963	16 350 000	3.6	138 720 000	30.2	83 423	26 360
1964	15 400 000	3.3	130 380 000	27.7	40 265	11 831
1965	17 390 000	3.6	109 840 000	22.8	33 402	9 058
1966	17 230 000	3.5	83 000 000	16.8	32 616	8 482
1967	18 560 000	3.7	96 450 000	17.2	84 902	26 225
1968	22 000 000	4.3	83 000 000	16.1	35 179	7 266
1969	22 700 000	4.3	76 870 000	14.6	19 281	4 156
1970	23 060 000	4.3	77 110 000	14.4	12 773	2 240
1971	24 190 000	4.4	91 680 000	16.7	16 190	2 706
1972	26 950 000	4.8	112 730 000	19.6	27 407	5 457
1973	24 840 000	4.4	112 340 000	19.8	88 114	15 434
1974	24 180 000	4.2	123 430 000	21.3	188 003	31 262
1975	19 025 474	3.2	86 718 634	14.6	1 436	176
1976	16 745 086	2.8	66 854 231	11.1	0	0

[a] The percentages provide an index of vaccination activity and are derived by dividing the reported total number of vaccinations performed by the estimated total population (from Basu et al., 1979). The figures do not provide a measure of the proportion of the population newly immunized or whose immunity was boosted. Vaccination was sometimes unsuccessful and some individuals were vaccinated two or more times in a year. Moreover, the reported total numbers of vaccinations performed were sometimes inflated.

The Herculean effort to eradicate smallpox through mass vaccination, launched so enthusiastically in 1962, had all but come to a halt by the time the Nineteenth World Health Assembly, in May 1966, decided to embark on the Intensified Smallpox Eradication Programme. The Indian delegate to the Health Assembly, commenting on the new initiative, pointed out that India would need 180 million doses of vaccine annually, of which it would never be able to produce more than 60 million doses, and expressed the hope that WHO could meet the projected deficit. He cautioned the delegates that unless good basic health services were developed "it would be very difficult indeed to maintain the immunological status temporarily reached" in a mass campaign (World Health Organization, 1966c).

In December 1966, Henderson, who had recently been appointed Chief of the newly constituted Smallpox Eradication unit at WHO Headquarters, arrived in New Delhi to participate in his first intercountry smallpox eradication seminar, attended by representatives from countries in WHO's South-East Asia Region. It was not an auspicious beginning, as India, which then accounted for one-third of the world's cases, announced at the seminar that it had terminated its attack phase and had reverted to a programme of maintenance vaccination.

The Intensified Smallpox Eradication Programme Begins, 1967

The advent of the Intensified Programme in India found a discouraged staff. Dr Lal, the director of the National Smallpox Eradication Programme since 1962, retired and, because the attack phase had been terminated, was not replaced. This left at the national level only one medical officer, Dr Mahendra Singh, a Deputy Assistant Director-General of Health Services. Although he was overwhelmed by the tasks of giving some sort of direction to the remaining smallpox control activities and of providing the necessary reports to Parliament among many other duties—Dr Singh tried valiantly to stimulate the host of vaccinators distributed across India. He dispatched numerous cables and letters asking state health directors to take action to control epidemics reported officially to him or, as often, through the press. Vaccination targets were established for each state and those who failed to meet their goals were given forceful reminders. The number of reported vaccinations diminished, however, from 139 million in 1963 and 130 million in 1964 to 96 million in 1967 (Table 15.4). Vaccine distribution was also Dr Singh's responsibility, and a continuing problem because reserves were few and requests to replenish vaccine stocks in state and district offices were often not forthcoming until supplies had been exhausted. Government regulations required that Dr Singh should travel by train or bus, often a 1- or 2-day trip to reach distant and populous state capitals. In each state, there was only one official responsible for smallpox, and he was usually assigned responsibility for one or more additional programmes. The smallpox eradication programme and its still extensive complement of vaccinators laboured under a severe shortage of senior, responsible staff.

Assessment of the Programme in India, October 1967

In 1967, smallpox incidence rose dramatically, eventually reaching a total of 84 902 cases, more than had been reported in any year since 1958. Concerned by this turn of events, the Indian government agreed that a joint India–WHO assessment team should

Plate 15.2. Medical officers at a primary health centre in Maharashtra State. *Right*: Mahendra K. Singh (b. 1928), a Deputy Assistant Director-General of Health Services, who was the only medical officer at the central level in India's National Smallpox Eradication Programme from 1966 to 1972 and sustained the momentum of the work until additional senior Indian and WHO staff could be assigned. He continued with the programme until the eradication of smallpox in India had been certified in 1977 and was later appointed Director of the Central Bureau of Health Intelligence.

appraise the situation and suggest how it might be rectified. The team's operations were planned and organized by Dr Jacobus Keja, the adviser on smallpox eradication in WHO's South-East Asia Region, and by Dr Singh. In India, an assessment such as this, in which WHO staff travelled to the field, was an uncommon event at that time. Most WHO advisers remained in New Delhi or occasionally visited the more populous state capitals, in which hotels were plentiful. When preparations were being made for the trip, it was discovered that the regional office had in its stores none of the commonly used Indian bedrolls that were needed when travellers stopped at government rest-houses.

The assessment team, comprising 8 senior national health officers and 8 WHO staff and consultants, spent 6 weeks in the field, from 8 October to 19 November. They visited Maharashtra and Uttar Pradesh, two states experiencing epidemic smallpox in 1967, as well as Punjab in the north-west, a state with moderate incidence, and the southern state of Tamil Nadu. The last of these states was of particular interest because of the very few cases reported (263 in 1967) among its population of nearly 40 million.

The observations made by the team are telling, as they provide an overview of the status of smallpox and of the programme in 1967. The team concluded that the programme "is still far from achieving its objective of smallpox eradication in most areas and ... in fact, a very considerable epidemic potential exists in India at the present time." The conclusions of its report are paraphrased below:

Supervision and direction

● The functions and responsibilities of the National Smallpox Eradication Programme from the central level to the periphery are fragmented among a variety of independent and semi-independent organizations. There is lack of clarity and definition of responsibilities and objectives at all administrative levels.

● The *central directorate* is inadequately staffed and has no effective mechanism for exercising clear guidance and direction of the programmes at state and local level. Its functions are limited to the collection from the states of inadequate data regarding smallpox incidence and the number of vaccinations performed, the distribution of imported freeze-dried vaccine, the occasional organization of meetings of state and local programme directors, the distribution of some health education material and liaison with international organizations.

● The *states* exhibit a great variation in organizational structure. In many, responsibility for the programme is given to a senior officer burdened with many additional responsibilities. With few exceptions, the state directorates act merely as channels for funding, the transmission of instructions and the receipt of periodic reports from the districts.

● In the *districts*, the district health officer has overall responsibility for the programme as one of many responsibilities. Although as many as 3 paramedical personnel act as assistants, field visits are infrequent, supervision is poor, morale is low, interest in the programme is fading and vaccine is improperly handled and stored. Vaccinators are superintended partly by local administrative bodies and municipal boards and partly by the district staff.

Programme execution

● *Legislation* regarding compulsory vaccination varies widely. In some states both primary vaccination and revaccination are required, while in others vaccination is not compulsory. The laws governing enforcement involve cumbersome procedures, and fines are minimal and rarely imposed.

● The *plan* calls for the vaccination of all newborn infants and other individuals not

Table 15.5. India: vaccinator productivity and salary costs per vaccination performed, 1967

	Number of blocks studied	Number of vaccinations performed per vaccinator per day (range)	Cost per vaccination[a] in rupees (range)
State:			
Maharashtra	10	6.3 (0.5–11.3)	2.42 (13.9–0.48)
Punjab	8	5.7 (0.1–12.7)	3.17 (13.2–0.42)
Tamil Nadu	11	24.5 (6.4–51.6)	0.49 (1.04–0.16)
Uttar Pradesh	19	11.4 (3.1–37.2)	0.94 (8.71–0.20)
Municipality:			
Bombay		14.3	0.47
Madras		8.5	..[b]

[a] Salary costs only—i.e., not including costs of vaccine, supervision, supplies or transport. (In 1967, 1 rupee was equivalent to US$0.13.)
[b] .. = data not available.

previously vaccinated and the revaccination of everyone every 3 years; it also requires an assessment of "takes" among all primary vaccinees and 50% of revaccinees, as well as entry in the family registers of actions taken. The team concludes that none of the targets is being reached and that records are being falsified in most areas visited.

- The number of *vaccinators* is high (ranging from 1 for every 26 000 persons in Maharashtra to 1 for every 31 000 in Uttar Pradesh) but productivity is low [Table 15.5]. The mean number of vaccinations performed per day ranges from 5.7 in Punjab to 24.5 in Tamil Nadu, but in some blocks the average is less than 1 vaccination per day. Vaccinator salary costs alone average 0.47 rupee (US$0.06) per vaccination, but in 3 blocks they exceed 7.5 rupees (US$0.98) per vaccination.
- *Supervision*, except in Tamil Nadu, consists primarily in determining whether or not the vaccinator reports for work.
- *Vaccine* is improperly stored, inventories are inaccurate and refrigerators are frequently lacking or not in working order.
- The number of *reported cases* is estimated to be no more than 10% of the actual number and notification is considerably delayed except in Tamil Nadu, in which reporting appears to be reasonably complete. Many cases which are officially notified to state authorities are not subsequently reported to the national authorities. This deficiency in notification is illustrated by the situation in Punjab, in which state records to date in 1967 showed 1370 cases, of which only 273 had been notified at the national level.
- *Containment* measures are insufficient. For example, in a village in Uttar Pradesh, with a population of 250, 20 cases occurred; after containment, it was found that 20% of the unaffected children remained unvaccinated.
- Contrary to the findings of other reports, *vaccination acceptance* is good and the number of refusals for religious reasons is negligible. For the most part refusals stem from the unwillingness of people to be vaccinated at a time when a serious reaction might interfere with occupational responsibilities. Contributory factors are the tactlessness of some vaccinators, a crude vaccination technique and failure to inform people of the importance of vaccination. The rotary lancets waste vaccine (15 vaccinations are obtained from a vial of 0.25 ml compared with the 25–50 vaccinations obtained when the scratch technique is used); the lancets are difficult and time-consuming to sterilize and produce unusually severe local reactions.
- *Vaccination take rates* are said to be 100%, but assessment from records was possible only in Bombay. The records there show a take rate of 99.7%, but, in fact, failures were being recorded only after 3 unsuccessful attempts. The records show a maximum take rate of 77% after a single vaccination but it is probable that the actual take rate is considerably lower.
- The *family registers* everywhere are incomplete and contain numerous errors. They have been abandoned in Uttar Pradesh; in the Punjab and Maharashtra, in which a serious effort is being made to use them, vaccinators spend more than half their time on keeping them up to date.

Levels of achievement

- Smallpox incidence, the ultimate yardstick for measuring success, is noted to be rising. The total number of cases by the end of 1967 will represent the greatest incidence to be recorded in a decade. Even so, this total will represent 10% or less of the actual incidence.
- Cases are occurring in all age groups, although two-thirds or more in the states assessed are found in individuals under 15 years of age [Table 15.6].
- The proportion of the population reported to be receiving primary vaccination each year is less than 4% in all 4 states. With an estimated birth rate of 4% and many children born in previous years remaining unvaccinated, it is apparent that the number of susceptible subjects is accumulating.
- Sample surveys conducted among individuals under 15 years of age in randomly selected districts of the 4 states and wards of the cities of Madras (Tamil Nadu) and Bombay (Maharashtra) reveal widely different levels of performance [Table 15.7]. Uttar Pradesh has a higher proportion of unvaccinated children than was found in a survey conducted 10 years ago. In contrast, 90% of those in Tamil Nadu and 87% of those in the Punjab have vaccination scars. Vaccination levels in Madras and Bombay are substantially better than in the non-urban areas, a result attributed, in part, to the vaccination of children at birth (nearly 80% of them are born in hospital).

The team offered a detailed series of recommendations prefaced by the statement: "The Central Government should develop a new and long-term strategy to meet the

Table 15.6. India: age distribution of cases of smallpox in 4 states, 1967

Age group (years)	Maharashtra	Punjab	Tamil Nadu[a]	Uttar Pradesh
<1	12%	10%	10%	16%
1–4	45%	21%	32%	30%
5–14	32%	33%	23%	35%
≥15	11%	36%	35%	19%
Number of cases	100	418	4 329	158

[a] Data pertain to 1965–1967.

Table 15.7. India: results of vaccination scar surveys in children in 4 states and 2 municipalities, by age group, 1967

	Number of districts or wards surveyed	<1 year		1–4 years		5–14 years		All
		Number examined	% with scar	Number examined	% with scar	Number examined	% with scar	% with scar
State:								
Maharashtra	5	609	38	1 612	77	2 122	90	79
Punjab	5	785	48	2 622	88	3 151	96	87
Tamil Nadu	5	406	39	1 553	93	2 038	99	90
Uttar Pradesh	9	897	10	3 428	56	4 824	85	69
Municipality:								
Bombay	5	383	69	1 034	90	1 132	96	89
Madras	6	465	73	1 620	97	2 196	99	95

problem." In brief, it recommended that greater emphasis should be given to case detection and the containment of outbreaks, especially during the summer months, when the incidence was lowest; and that primary vaccination, including the vaccination of newborn infants, should be given priority. An increase in the personnel complement of the national directorate from 1 to 5 professionals and a concomitant extension of their scope of responsibility were also recommended, along with the strengthening of supervision at all other administrative levels. It was suggested that vaccine production should be centralized and financed under national rather than state authority, that the use of liquid vaccine should cease throughout India, that the bifurcated needle should replace the rotary lancet, and that the family registers should be abolished.

Progress Achieved in the Programme, 1968–1970

The recommendations of the joint assessment team were basically sound but smallpox eradication was not high among the government's priorities. Nevertheless, over the succeeding 3 years, the production of freeze-dried vaccine increased and its quality was improved, many laboratories producing liquid vaccine were closed, the bifurcated needle was introduced, the number of primary vaccinations increased, the vaccination of newborn infants was initiated in several areas, and in some states effective surveillance–containment programmes were conducted.

Vaccine and the vaccination programme

On the basis of WHO recommendations, Dr Singh stressed in a number of directives the importance of primary vaccination, and, as from 1968, the proportion of the population reported to have been given primary vaccination increased significantly (see Table 15.4). However, even with the increase, this proportion barely exceeded the birth rate. At the same time, the total number of reported vaccinations declined steadily.

The vaccination of infants at birth was recommended as a national policy. Traditionally, primary vaccination in India had been deferred until children reached at least 3 months of age. Studies begun in 1959 by Dr A. R. Rao in Madras showed that the vaccination of neonates was safe and that systemic symptoms were minimal (Rao & Balakrishnan, 1963). With the liquid vaccine then in use, 80% were successfully vaccinated but, when freeze-dried vaccine and the bifurcated needle became available, this rate rose to more than 95%. It was clear that if vaccinators could vaccinate all children whom they encountered, overall vaccinial immunity would be enhanced. Equally important, higher levels of vaccinial immunity could be achieved in large urban areas, where 75–80% of women were delivered in a hospital or nursing home. Because the high concentration of people in urban areas played an important role in sustaining smallpox transmission, it was hoped that routine vaccination of newborn children in cities might have a significant impact in diminishing incidence throughout the country.

The routine vaccination of neonates began in Madras and Bombay in 1967 and in several other cities of Tamil Nadu in 1968. However, the practice was not enthusiastically pursued in most areas, partly because of the lack of interest shown by the autonomous municipal health officers and partly because mothers were reluctant to let their babies be vaccinated. They had observed in other children

the severe lesions induced by the rotary lancet and had had no opportunity to see the results of vaccination with the bifurcated needle.

From 1968 to 1970, efforts were made to increase the volume and quality of vaccine produced in India and to improve the distribution system and storage of the product. In 1969 the government appointed a central director for vaccine production and distribution, Dr S. N. Ray, and the following year, the 4 vaccine production centres were placed under central government authority and financed by central government funds rather than state funds. This simplified distribution, because vaccine produced in any one of the institutes could then be sent to any state of India without special payments being required. Previously, vaccine produced in each of the state laboratories had been used mainly in that state, while vaccine donated to India, primarily by the USSR, was sent to other states.

Vaccine production in India gradually increased in volume but less rapidly than had been expected. Not until 1974, in fact, did the country become completely self-sufficient (Table 15.8). In part, the delays could be attributed to preoccupation on the part of the director of the Patwadangar laboratory, the principal production laboratory, with the introduction of comparatively new, more elaborate machines for freeze-drying—the so-called shelf-driers. Relatively simple centrifugal freeze-driers were then in use in many countries and when installed in competent laboratories, as in Indonesia and Kenya for example (see Chapter 11), could be used at full capacity within a year. The director justified the need for the shelf-driers on the grounds that extremely large quantities of vaccine would be required, estimating the need for far greater amounts than had been used during the 1962–1966 mass vaccination campaign. Moreover, he argued that the bifurcated needles, although they used less vaccine and had been adopted in most other countries, would never be acceptable in India. WHO smallpox eradication programme staff, however, foresaw the need for smaller quantities of vaccine, especially if the bifurcated needles could be used, and argued for the purchase of the less complex centrifugal driers. After an impasse lasting almost a year, a staff member of the WHO regional office, who was responsible for providing advice to laboratories, gave approval for the purchase of the shelf-driers, although he himself was not competent in vaccine production. With the promise of purchase of the shelf-driers, the laboratory director gave approval for studies of the bifurcated needle to be undertaken in India (see below). As had been feared, the shelf-driers proved difficult to operate and production increased only slowly but, because of the introduction of the bifurcated needle and the continued provision of vaccine by the USSR, vaccine shortages did not occur.

With an assured supply of freeze-dried vaccine available throughout India, it became possible for the government to insist on the cessation of production of the thermolabile

Table 15.8. India: number of ampoules[a] of freeze-dried vaccine produced each year, 1962–1977, by vaccine production centre, and donated vaccine distributed, 1970–1974

Years	Patwadangar	Belgaum	Guindy (Madras)	Hyderabad	Total	Donated vaccine[b]
1962–1963	38 368	0	0	0	38 368	
1963–1964	87 121	0	609	0	87 780	..
1964–1965	480 208	0	5 418	0	485 626	..
1965–1966	1 202 296	0	212 565	0	1 414 861	..
1966–1967	858 889	172 000	380 639	0	1 411 528	..
1967–1968	959 931	620 155	557 867	173 685	2 311 638	.
1968–1969	1 188 680	1 123 031	852 667	401 827	3 566 205	.
1969–1970	1 077 385	812 383	470 000	466 759	2 826 527	..
1970–1971	829 054	498 337	1 114 000	244 657	2 686 048	1 823 000
1971–1972	1 185 385	1 164 037	792 662	381 434	3 523 518	1 650 000
1972–1973	2 765 181	1 447 573	1 204 684	442 398	5 859 836	2 100 000
1973–1974	4 054 862	2 317 641	1 627 417	807 542	8 807 462	1 300 000
1974–1975	3 298 075	3 174 857	1 886 277	1 065 035	9 424 244	0
1975–1976	2 853 113	1 908 252	1 721 082	691 073	7 173 520	0
1976–1977	1 545 918	1 888 716	1 628 057	569 657	5 632 348	0

[a] With the rotary lancet, the contents of 1 ampoule were required to vaccinate 12–15 persons. When the bifurcated needle was used, the same quantity of vaccine sufficed to vaccinate as many as 100.

[b] The USSR donated from 5 to 6 million ampoules of vaccine annually beginning in 1962, but data regarding the distribution of this vaccine are not available before 1970–1971.

liquid vaccine. However, closure of the 14 state institutes which produced it proved to be difficult. The central government lacked the necessary authority; one by one, each state and centre had to be visited by officials of the central government and persuaded to cease production. This was finally accomplished in 1970, the last centres being in Calcutta and the eastern states. Even after closure of the production centres, however, problems remained. In several states, the stocks of liquid vaccine occupied all the available refrigerated storage space and, without the sanction of the finance department to destroy the vaccine, programme officers could take no action. Accordingly, in several areas, including Bihar State, in which smallpox was eventually to prove a major problem, stocks of freeze-dried vaccine continued to be stored at room temperature while the obsolete liquid vaccine was kept under refrigeration.

The provision of satisfactory refrigerated storage for vaccine was a continuing problem in other areas as well. The freeze-dried vaccine was supposed to be kept at ambient temperature for not more than 30 days but could be stored almost indefinitely at temperatures of 4 °C or less. Because, for reasons of logistics, most vaccinators could obtain vaccine supplies only once a month, it was important to ensure that vaccine stored in district offices, as well as in the state and national depots, was kept under refrigeration. Satisfactory storage at state and national distribution centres was gradually achieved through the provision of refrigerators by UNICEF and WHO and through the use of other facilities such as cold-rooms normally used for the storage of fruit and vegetables. In the districts, however, satisfactory storage was uncommon. Although virtually all district offices were provided with refrigerators for the storage of drugs and vaccines for a variety of programmes, few were maintained in working order. For example, as late as 1975, 85% of the refrigerators in district offices in Uttar Pradesh were found to be inoperative. Fortunately, as tests of vaccine showed, much of the vaccine produced in the USSR and India maintained levels of potency adequate for primary vaccination even after 3–4 months at high ambient temperatures (Sehgal, 1974; Sehgal & Ray, 1974).

The assessment team had also recommended that at least one-third of all batches of vaccine produced and tested in the separate laboratories should be independently tested by a national vaccine control laboratory and that the results should be confirmed by a WHO smallpox vaccine reference centre (National Institute of Public Health, Bilthoven, Netherlands). In 1969, an Indian central control laboratory was established at the National Institute of Communicable Diseases, New Delhi, although it was not until 1972 that the laboratory actually monitored the recommended number of batches. In 1969, some batches of vaccine also began to be sent to the WHO reference centre for testing. During the period 1969–1976, of the 241 batches tested by WHO only 9 (3.7%) were found to be substandard (Basu et al., 1979). Although these data would suggest a consistently high level of satisfactory production, it must be noted that all batches dispatched to WHO had been determined, first by the production laboratory and then by the central control laboratory to be completely satisfactory. The producers and the central testing laboratory found a much higher proportion of batches of vaccine to be of inferior potency or stability or unacceptably contaminated with bacteria. Some such batches were destroyed but, in the first few years, most were distributed anyway because vaccine was in short supply. Properly, it was considered preferable to use substandard freeze-dried vaccine than to use liquid vaccine or to have no vaccine at all. No compilation of data on vaccine quality is available, but it was known that the Hyderabad and Guindy laboratories both had persistent difficulties in producing satisfactory vaccine. However, together they accounted for less than one-fifth of all vaccine distributed in India and most of the vaccine they produced was distributed to states in southern India in which health services were generally better and smallpox incidence was lower.

The improved quality of vaccine and a better storage system undoubtedly resulted in a higher proportion of successful vaccinations in the field, although no data are available to substantiate this.

Introduction of the bifurcated needle

The bifurcated needle had been tested by WHO in late 1967 and early 1968 and was rapidly made available throughout most countries by the middle of 1968. In India, however, the traditional rotary lancet had

been in use since before the turn of the century and a number of prominent senior health authorities as well as the director of the vaccine production laboratory in Patwadangar resisted the introduction of the new instrument. They argued that it would produce fewer successful vaccinations, that vaccinators would find it too difficult to use, and that the population would resist vaccination with an unfamiliar device. Finally, it was agreed that comparative studies of the two instruments would be undertaken by the National Institute of Communicable Diseases and the Central Health Education Bureau (WHO/SE/70.16).

In 1969, the National Institute assessed the efficacy of the two techniques (Pattanayak et al., 1970). In one study, previously vaccinated children were vaccinated on one arm with the rotary lancet and on the other arm with the bifurcated needle. Vaccines of three different levels of potency were employed. The results showed that the bifurcated needle had a clear-cut advantage over the rotary lancet (Table 15.9).

Comparative data derived from a study of a small number of children given primary vaccination showed similar results. It was found that vaccinators readily learned the new technique and used it successfully.

During the same period, the Central Health Education Bureau investigators assessed the acceptability of the new technique, with surprising results. Persons in 5 villages were vaccinated with the bifurcated needle, but they were given no explanation about the new device. One week later, the vaccinees were examined to determine the proportion with successful vaccinations and were interviewed about the new technique. All those given primary vaccination, and 79% of those who had been revaccinated, had successful takes. As the investigators noted, "surprisingly, few realized that the technique applied was different from the customary rotary lancet method" (WHO/SE/70.16). With these results, the needle was accepted by the national health authorities for use in India.

Needles were provided by WHO in large numbers and, by late 1969, they were in wide use in many states. However, the adoption of the new technique required that a decision should be taken separately by each state and municipality, and some were not persuaded. Not until 1971, for example, were the needles used in the states of Uttar Pradesh and Bihar. In many municipalities, vaccinators continued to use the rotary lancet until late 1973, when municipal smallpox eradication staff were brought under state jurisdiction.

The use of the bifurcated needle, however, brought a curious and unforeseen administrative problem. Auditors in India continually scrutinized the number of vaccinations performed in an area and compared it with the number of vaccinations reported in order to detect wastage. The vials of vaccine containing 0.2 ml allowed for only 15 vaccinations if the rotary lancet was used. With the bifurcated needle as many as 100 vaccinations could be performed with the contents of one vial, but in practice, an average of only 40–50 vaccinations was achieved because whatever reconstituted vaccine remained at the end of the day was supposed to be discarded. Although, in fact, more vaccinations were performed per vial supplied, the auditors calculated that each vial should now yield 100 doses of vaccine. Their assertions that vaccine was being wasted were to plague smallpox eradication staff throughout the rest of the programme.

Sample surveys to determine vaccination status

In 1969, the technique for vaccination scar surveys which had been developed in Afghanistan (see Chapter 14) was introduced into India. Through such surveys it was hoped that responsible officials would identify for themselves deficiencies in their vaccination programmes and correct them.

Table 15.9. India: results of simultaneous revaccination of children with the rotary lancet and the bifurcated needle

Vaccine potency (pock-forming units/ml)	Number of children	Rotary lancet	Bifurcated needle
		Number (%) with satisfactory response	Number (%) with satisfactory response
1×10^8	84	22 (26)	47 (56)
5×10^7	82	10 (12)	29 (35)
1×10^7	81	10 (12)	26 (32)

The simplified methodology for scar surveys, using a cluster sample technique, was enthusiastically received in many states and numerous surveys were undertaken, some of which were state-wide. Not all the surveys were well designed, but the results consistently revealed a remarkably high proportion of vaccinated persons. The surveys showed that vaccination scars were borne by 92–99% of individuals in the age group 5 years and above; by 78–92% of those aged 1–4 years; and by 10–60% of infants under 1 year. Although the results were dutifully compiled and reported, few used the data constructively to identify populations or areas in which vaccinial immunity was low and to improve performance in such areas. The idea of assessing vaccination status in this way was reasonable but, in retrospect, the approach was probably counter-productive in that it served to reinforce the notion that mass vaccination was the principal foundation of the programme, rather than surveillance–containment measures.

The decline in smallpox incidence

Between 1967 and 1970, the reported number of smallpox cases fell dramatically—from 84 902 to 12 773, the lowest total ever recorded in India. Both government and WHO staff recognized that this reflected, at least in part, the normal periodic fluctuations of smallpox. Peaks in smallpox incidence in India normally occurred every 4 7 years, a periodicity extending back many decades. The peak in 1967 occurred just 4 years after the peak in 1963, which had been preceded, 5 years before, by the peak in 1958. This pattern was said to occur as a result of the gradual increase in the number of susceptible persons because of the waning of immunity in the population at large and the addition of susceptible newborn children. It was believed that when a sufficient number of susceptible persons had accumulated, an epidemic would ensue which would diminish this pool of susceptible individuals and thus the ease with which smallpox could spread. Following the epidemic, smallpox incidence would again decline. The decrease in the number of reported cases between 1967 and 1970 was thus not unexpected, but because the incidence had fallen to such low levels, some government and WHO staff were both optimistic and, to a certain extent, unduly satisfied with progress in the redirection of the programme. The archaic notification system, with its delays in reporting, only served to reinforce this optimism. By mid-January 1971, for example, only 8026 (63%) of the 12 773 cases eventually recorded for 1970 had been reported to the Central Bureau for Health Intelligence.

Southern India, 1967–1970

The decline in smallpox incidence between 1967 and 1970 was especially notable in the 6 states and 5 union territories which formed the entire southern part of India. This area had a population in 1967 of 196 million (38% of the national total). The number of cases fell from 42 633 in 1967 to only 795 in 1970. Many districts reported no cases in that year (Fig. 15.5) and none was detected in the entire state of Tamil Nadu (population, 41 million) (Table 15.10).

In part, this decline was attributable to a generally more developed health service structure, especially in the states of Kerala and Tamil Nadu and, in consequence, a better execution of the mass vaccination campaign. It was also associated with the development of an effective surveillance–containment programme—first in Tamil Nadu and later in parts of Andhra Pradesh.

To evaluate the applicability of surveillance–containment in India, it was decided in 1968 to investigate and contain all outbreaks in Madras, the capital of Tamil Nadu, and subsequently in the state itself, employing a surveillance team directed by Dr A. R. Rao, then Health Officer of the Madras Municipal Corporation. Support for this operation was provided by the Indian Council for Medical Research and WHO (WHO/SE/68.6 and WHO/SE/68.7, A. R. Rao). Dr Rao, for many years the Director of the Madras Infectious Diseases Hospital, had conducted extensive investigations into the clinical and epidemiological behaviour of smallpox (Rao, 1972). He was an ideal person for the task and interested in taking up the challenge.

Smallpox incidence in Tamil Nadu had declined sharply, from 8901 cases in 1963 to only 263 cases in 1967, of which 38 cases had been reported by the Madras Municipal Corporation. The joint India–WHO assessment team (1967) believed that reporting was better in Tamil Nadu than elsewhere in India and, if indeed there were as few cases as notifications suggested, it should be possible to stop transmission with a comparatively

modest outbreak containment programme. If successful, it would serve as an example for other states in India.

Between January and June 1968, the season of highest smallpox transmission, Dr Rao investigated 13 outbreaks in Madras, which were detected when patients were brought to the hospital or when fatal cases were registered at the burial grounds. The source of 7 outbreaks could be traced, 6 of them coming from adjoining states. Eight of the index cases were hospitalized within 10 days of onset and none of them spread the disease. Five of the infected persons were hidden at home and, before discovery, 8 second generation and 4 third generation cases occurred. However, the total number of cases was small and, as Dr Rao emphasized, smallpox did not spread rapidly in this population despite its high density and the season of the year. In mid-

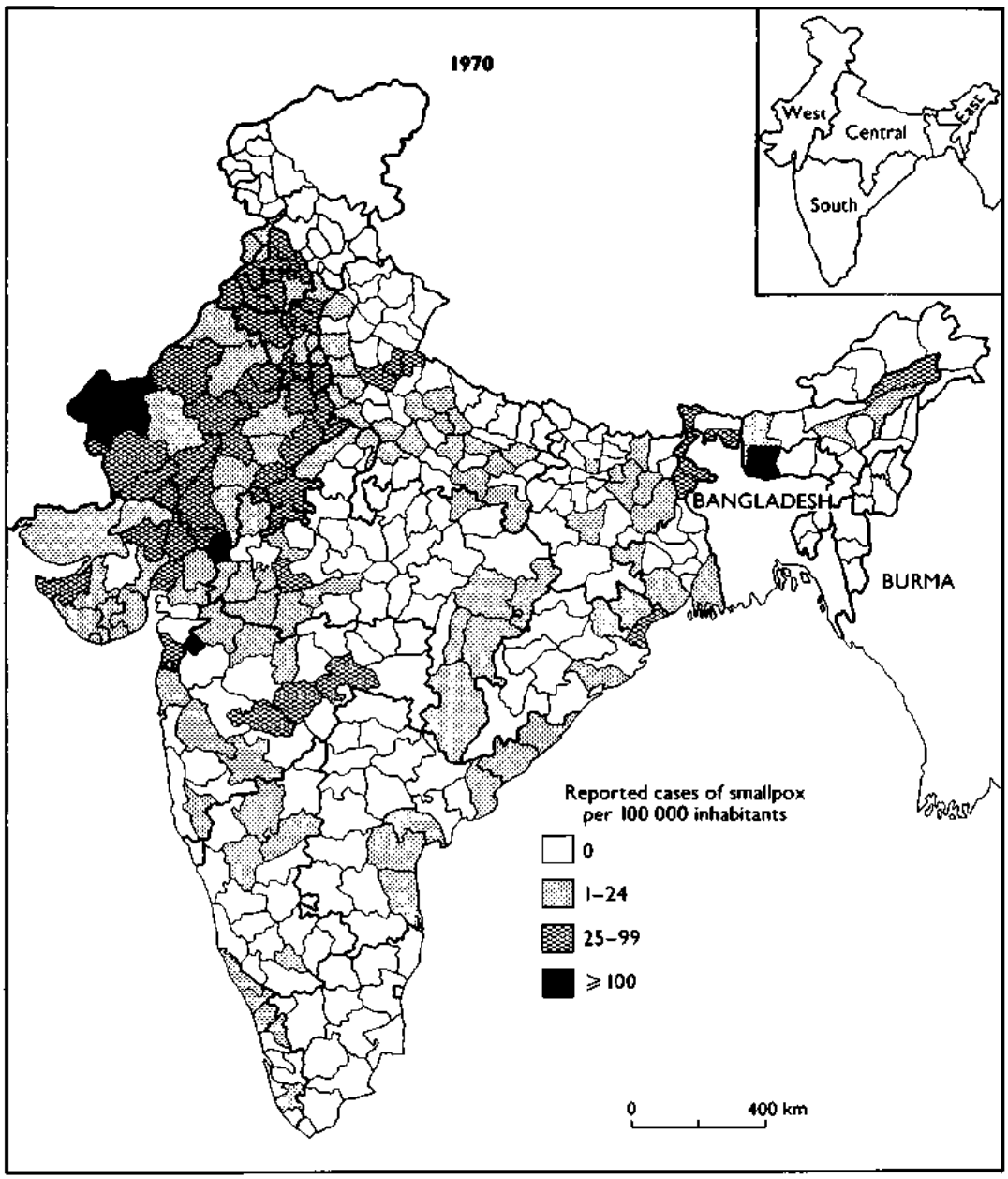


Fig. 15.5. India: number of reported cases of smallpox per 100 000 inhabitants, by district, 1970.

Table 15.10. Southern India: number of reported cases of smallpox, 1967–1970

State or union territory[a]	1967	1968	1969	1970
Andhra Pradesh	8 618	7 951	1 893	358
Dadra and Nagar Haveli	18	2	0	0
Goa, Daman and Diu	45	18	12	1
Kerala	152	2	9	31
Maharashtra	27 961	3 173	1 411	174
Mysore[b]	1 770	981	178	126
Orissa	3 806	3 200	1 247	105
Tamil Nadu	263	150	6	0
Total, southern region	42 633	15 477	4 756	795
Other states and union territories of India	42 269	19 702	14 525	11 978
Grand total	84 902	35 179	19 281	12 773

[a] No cases were recorded during this period in the union territories of Andaman and Nicobar Islands, Lakshadweep and Pondicherry.
[b] Became the state of Karnataka late in 1973.

June, the team began to extend its activities beyond the boundaries of the city. The investigation of a case brought to the hospital from a village 24 kilometres away revealed an outbreak of 44 cases in 5 villages. The outbreak had begun in January, when migrant workers returned from the neighbouring state of Andhra Pradesh. As in the city, smallpox had spread surprisingly slowly, suggesting again that outbreaks might be readily controlled. Between July 1968 and June 1969 only 2 additional outbreaks were found in all of Tamil Nadu: one comprised 6 cases imported from Madhya Pradesh State, and the other involved a single patient who had been infected in Gujarat State (WHO/SE/70.19, A. R. Rao). Transmission in Tamil Nadu had been interrupted less than 6 months after a single surveillance team had begun its work; after May 1968 the state remained smallpox-free except for importations.

The Madras team had little to do and so, in October 1969, with the agreement of the authorities in the neighbouring state of Andhra Pradesh (population, 43 million), Dr Rao investigated outbreaks in coastal villages 160 kilometres north of Madras. In all, he documented more than 200 cases in the poorly vaccinated population of a group of fishing villages (WHO/SE/70.17, A. R. Rao et al.). This, in turn, stimulated surveillance activity on the part of the state authorities of Andhra Pradesh. The number of cases in Andhra Pradesh diminished from 7951 in 1968 to 1893 in 1969 and to 358 in 1970. However, transmission persisted, primarily among the fishermen and their families, who migrated seasonally from this area northwards to Orissa State.

The success of surveillance and containment measures in both Andhra Pradesh and Tamil Nadu was dramatic, but, despite Dr Rao's presentations at subsequent national and international meetings, little notice was taken of the achievement. The state smallpox eradication programme officer who accompanied Dr Rao to the meetings rightly noted that the vaccination campaign in Tamil Nadu had been exceptionally well executed, but he argued that it was for this reason, and not because of the surveillance–containment activities, that transmission had been interrupted there. Authorities in other states dismissed the attainment as not surprising in the generally more prosperous southern states and of no applicability to most of the rest of India.

Western India, 1967–1970

Although progress in southern India gave cause for optimism, the number of reported cases of smallpox doubled in the western state of Gujarat (population, 27 million), increasing from 3403 cases in 1967 to 7654 in 1968. The epidemic continued into 1969, when 6284 cases were recorded—i.e., one-third of all cases reported in India (Table 15.11) and, in fact, almost one-fifth of all cases reported throughout the world.

WHO proposed to the government of India that a team should visit Gujarat to assess the situation. The government agreed, albeit reluctantly, to a 1-week field trip. Since the 1967 India–WHO assessment of the programme, field visits by WHO Regional Office staff, although resident in New Delhi, had been discouraged. It was the government's view that WHO staff could

Table 15.11. Western India: number of reported cases of smallpox, 1967–1970

State or union territory	1967	1968	1969	1970
Chandigarh	12	0	0	9
Delhi	472	70	28	96
Gujarat	3 403	7 654	6 284	2 492
Haryana	4 809	633	683	2 161
Himachal Pradesh	44	2	0	1
Jammu and Kashmir	40	1	7	0
Punjab	1 393	76	228	234
Rajasthan	4 506	1 923	1 439	4 097
Total, western region	14 679	10 359	8 669	9 090
Other states and union territories of India	70 223	24 820	10 612	3 683
Grand total	84 902	35 179	19 281	12 773

contribute little to a programme that was directed by a national staff who had been engaged in eradication since 1962. Field visits by national staff were likewise uncommon, Dr Singh rarely being able to leave New Delhi because of his innumerable responsibilities. Moreover, his authority was circumscribed because the responsibility for programme execution rested primarily with the states.

In April 1970, a 3-man team, comprising Dr Andrzej Oles, from the WHO Regional Office for South-East Asia, Dr Singh and Henderson, visited Gujarat State and its capital, Ahmedabad (population, 1.7 million). The epidemic in Ahmedabad was considered by local staff to have begun in November 1969 and, to combat it, 150 temporary vaccinators had been hired to supplement a staff consisting of 1 supervisor (medical officer), 39 vaccinators and a 6-man "flying squad". This provided 1 vaccinator for approximately every 9000 persons. The hiring of large numbers of temporary vaccinators without additional supervisors was a common response throughout India to epidemic smallpox. Between January and March 1970, more than 360 000 people had been vaccinated but the number of reported cases continued to increase. The Deputy Director of Health and Medical Services, Dr G. J. Ambwani, had done a commendable job in improving the facilities for vaccine storage and distribution and in introducing the bifurcated needle. Vaccinial immunity was found to be high in all areas which the team visited. The containment of outbreaks was prompt but poorly executed. The team found many additional unreported cases and in none of the outbreaks had an effort been made to identify the source of infection and, thereby, additional outbreaks. Although local civil authorities were responsible for case reporting, almost all the cases were reported by vaccinators.

More disturbing was the discovery that the large numbers of cases reported were not reflected in reports to the national authorities. It was found that the Central Bureau for Health Intelligence had recently informed state statistical sections that it wanted a final report from all districts within 3 weeks of the notification of an outbreak. In Gujarat, this was interpreted to mean that any additional cases that were found after this period or any cases that had experienced the onset of illness more than 3 weeks previously should not be reported to the Central Bureau. The cases were, however, recorded by the state's smallpox eradication programme office. Not only was the epidemic in Gujarat of a far greater magnitude than had been suspected, but the discovery that this new policy had been adopted led to the suspicion that India's remarkable decline in incidence might possibly be an artefact caused by a reporting system distorted by misguided or misunderstood directives.

The team concluded that cases were occurring predominantly among a small, unvaccinated segment of the population, amounting to not more than 5–10% of the total, primarily in slum areas and among migrant labourers.

After just 5 days' work in the field, Dr Ambwani realized that he had not previously understood the surveillance–containment strategy and promised to implement such a programme forthwith. Working with the state smallpox eradication programme officer, Dr S. D. Verma, he was remarkably successful. The numbers of cases declined rapidly and in June 1971, only 14 months after the team's visit, transmission ceased.

Plate 15.3. Members of an Indian/WHO team to assess the smallpox epidemic in Gujarat State in April 1970. *Left to right*: Andrzej J. Oles (b. 1923), an epidemiologist with the WHO Regional Office for South-East Asia; Mahendra K. Singh; and G. J. Ambwani, Deputy Director of Health and Medical Services of Gujarat State.

Other cases occurred later but they were traced to importations from other states. The success in Gujarat suggested to both senior Indian and WHO staff that if states were given modest assistance to foster surveillance–containment programmes, these results might be replicated elsewhere. Unfortunately, Gujarat, like Tamil Nadu, was to prove an exception.

The team returned to New Delhi encouraged by Dr Ambwani's interest in and responsiveness to the surveillance–containment strategy but now less confident that the remarkable decline in the number of reported cases was real. A recommendation was made that the reporting system should be changed but this was vigorously resisted by the director of the Central Bureau for Health Intelligence. Thus, the programme continued, its personnel less certain of the true incidence of smallpox but now placing increased reliance on data provided by state eradication programme officers rather than on official government statistical reports. However, because the quality of the programme officers varied greatly from state to state and because the Central Bureau's directives were variously interpreted by officials at different levels, it was difficult to known what the different sets of numbers really meant without field visits to every state—and no staff were available to undertake such visits.

Yet another disturbing observation was made in the western states in the spring of 1970. It began to appear that smallpox might be moving as an epidemic wave in a clockwise direction around India. In 1967, immediately before the 1968–1969 Gujarat epidemic, Maharashtra, the state immediately to the south, had reported especially severe epidemics. That year, it had recorded 27 961 cases, one-third of all cases reported from India. The number dropped to 3173 in 1968 and to 1411 in 1969. In the spring of 1970, the states of Rajasthan and Haryana, immediately to the north of Gujarat, began to experience major epidemics.

This had not been expected. Since the 19th century, major epidemics in the Indian subcontinent had been observed to occur every 4–7 years, but the periodic fluctuations had been thought to take place more or less simultaneously throughout the country. The wider availability of vaccine had not altered this pattern. That the periodicity had persisted until 1962 was understandable because intensive and widespread vaccination had been conducted during and immediately after epidemics, but as smallpox waned so did interest in vaccination. However, it was quite unexpected that the intensive ongoing national vaccination campaign begun in 1962 had not prevented the 1967 epidemic. To explain this recurrence, it was suggested that many states had not conducted effective

campaigns, and because much of the vaccine used had lacked potency, the large pool of susceptible persons had not significantly diminished. Between 1967 and 1970, however, most of the vaccine reaching recipients was believed to be fully potent and because the number of primary vaccinations had substantially increased, the opinion was held that India should not again experience a major epidemic year. Thus, the recurrence of epidemic smallpox, apparently moving in a clockwise direction around India, was totally unexpected but a critical factor in the formulation of subsequent strategy.

In 1970, senior national government staff began to take a greater interest in the smallpox eradication programme. Epidemic areas in Haryana and Rajasthan abutted on New Delhi, the national capital. Reports of the outbreaks appeared in increasing numbers in New Delhi newspapers, and members of Parliament expressed concern through "call-attention" motions, obliging the government to give an account of what was being done.

The Gujarat team had concluded in its recommendations to the government: "... of greatest importance ... is the need to augment the staff at state level to provide leadership to the programme and to develop and coordinate, by active field work, the very critical surveillance–containment activities." WHO proposed to the government that 4 WHO epidemiologists should be recruited to work as advisers with state programme officers. One would be assigned to Rajasthan, in which smallpox incidence was rapidly rising; one each would be allocated to Uttar Pradesh and Bihar, the two densely populated states comprising most of the northern Ganges river plain, and, if assumptions regarding the clockwise movement of epidemic smallpox were correct, the next to experience major epidemics; the fourth epidemiologist would be assigned to work with state programme officers throughout the southern states in an effort to interrupt transmission in this vast area. Dr Singh, meanwhile, would plan to work with programme officers in the small neighbouring states of Haryana, Punjab and Himachal Pradesh as well as the Delhi Municipal Corporation.

The Director-General of Health Services and the Secretary of Health were initially of the opinion that 2 advisers would suffice but ultimately agreed to 4. On 9 September 1970, an agreement was signed by the government and WHO which committed WHO to provide: (1) 4 epidemiologists and 3 short-term consultants for 3 months each in 1970 and 1971, plus the costs of their travel; (2) vehicles and other supplies; and (3) funds to pay salaries, travel and per diem "for additional personnel employed full-time in smallpox units at the national and state levels up to the limit of Rs. 1 125 000 each year" (US$146 250). In 1970, WHO support to the programme for the first time exceeded US$100 000. During the succeeding 7 years, more than US$11 million would eventually be provided, most of which represented contributions from the government of Sweden (Table 15.12). Additional funds were allocated to the WHO Regional Office for South-East Asia, which as the Indonesian programme concluded, began to devote more time to the programme in India.

The Foundations are Laid for the Intensified National Campaign, 1971–1973

From 1971 until the summer of 1973 the programme gradually evolved and, in doing

Table 15.12. India: estimated expenditure[a] for smallpox eradication, 1965–1977, by source (thousands of US$)[b]

Year	India		WHO	Other[c]	Total
	Central government	State government			
1965	2 000	6 000	21	0	8 021
1966	2 000	6 000	19	0	8 019
1967	2 000	6 000	36	405	8 441
1968	2 000	6 000	45	0	8 045
1969	2 000	6 000	5	0	8 005
1970	2 179	6 000	182	0	8 361
1971	2 673	6 000	267	0	8 940
1972	4 128	6 000	352	0	10 480
1973	3 801	5 921	505	0	10 227
1974	4 516	5 625	2 522	483	13 146
1975	4 954	5 488	4 466	594	15 502
1976	4 556	5 000	2 642	0	12 198
1977	5 000	5 000	1 005	–	11 005
Total	41 807	75 034	12 067	1 482	130 390

[a] Expenditures by the central government (1965–1969) and state governments (1965–1972) are estimates. Of funds expended by WHO between 1974 and 1977, US$0.1 million were provided by the Swedish International Development Authority.

[b] Excludes the estimated value of vaccine provided between 1965 and 1974, which amounted to 701 million doses from the USSR and 5 million doses from WHO.

[c] Value of contributions in cash and in kind from Tata Industries (US$600 000), USA (US$402 000), UNICEF (US$380 000), and OXFAM (US$100 000).

Plate 15.4. **A**: Alberto M. Monnier (1914–1979), an epidemiologist, served as the WHO smallpox officer in Rajasthan State from 1971 to 1976. **B**: Viatcheslav A. Moukhopad fulfilled the same role in Uttar Pradesh State from 1971 to 1976.

so, laid the foundations for the intensified national campaign, termed "Smallpox Zero", which began in the autumn of 1973. A closer working relationship was established between the government of India and WHO; the bifurcated needle replaced the rotary lancet in all but a few municipal corporations; the use of liquid vaccine ceased completely; larger quantities of good-quality freeze-dried vaccine produced in India became available; the reporting system was changed; and a procedure for the detection of cases was elaborated.

WHO recruited 2 new regional smallpox advisers, for what was then called the Regional Epidemiological Surveillance Team, as well as 4 epidemiologists for assignment to India. Dr Nicole Grasset, a French virologist and epidemiologist, became the regional adviser in 1971, replacing Dr Keja, who had been transferred to Indonesia. She had worked previously in smallpox and measles control activities in eastern Nigeria and had proved to be a charismatic leader. She was joined in the regional office in 1972 by Ježek as the second regional adviser. Although they were responsible for smallpox eradication activities throughout the South-East Asia Region, much of their work was to be devoted to the programmes in India and Nepal. The 4 epidemiologists for the programme in India were assigned to the states. Dr Alberto Monnier, a Mexican epidemiologist who had been with the Indonesian smallpox eradication programme, began work in Rajasthan in January 1971 and Dr V. A. Moukhopad, a Soviet epidemiologist, arrived a month later to begin work in Uttar Pradesh. That summer, a Czech epidemiologist, Dr Vladimir Zikmund, began work in the southern states. Another epidemiologist reported for duty in Bihar during the summer but stayed only 6 months before resigning. At that time, the post in Bihar was felt to be the least critical, since the available data for 1971 showed smallpox was then concentrated in the north-western part of the country (Fig. 15.6), geographically distant from Bihar. A principal problem in Bihar, as well as in the other states, was the stipulation that each state should provide a vehicle for each adviser and cover the costs of its operation. Rarely before had WHO staff been assigned to work at state level in India and, with vehicles in the states in short supply and poorly maintained, the provision of transport for the advisers was a problem. In Bihar, none was made available and, in general, state officials showed little interest and offered the minimum of cooperation in helping to solve difficulties of this kind. Not until 2 years later were the inadequacies of the Bihar health structure fully appreciated. Conceivably, more energetic measures in Bihar at that time might have averted the catastrophe that lay ahead.

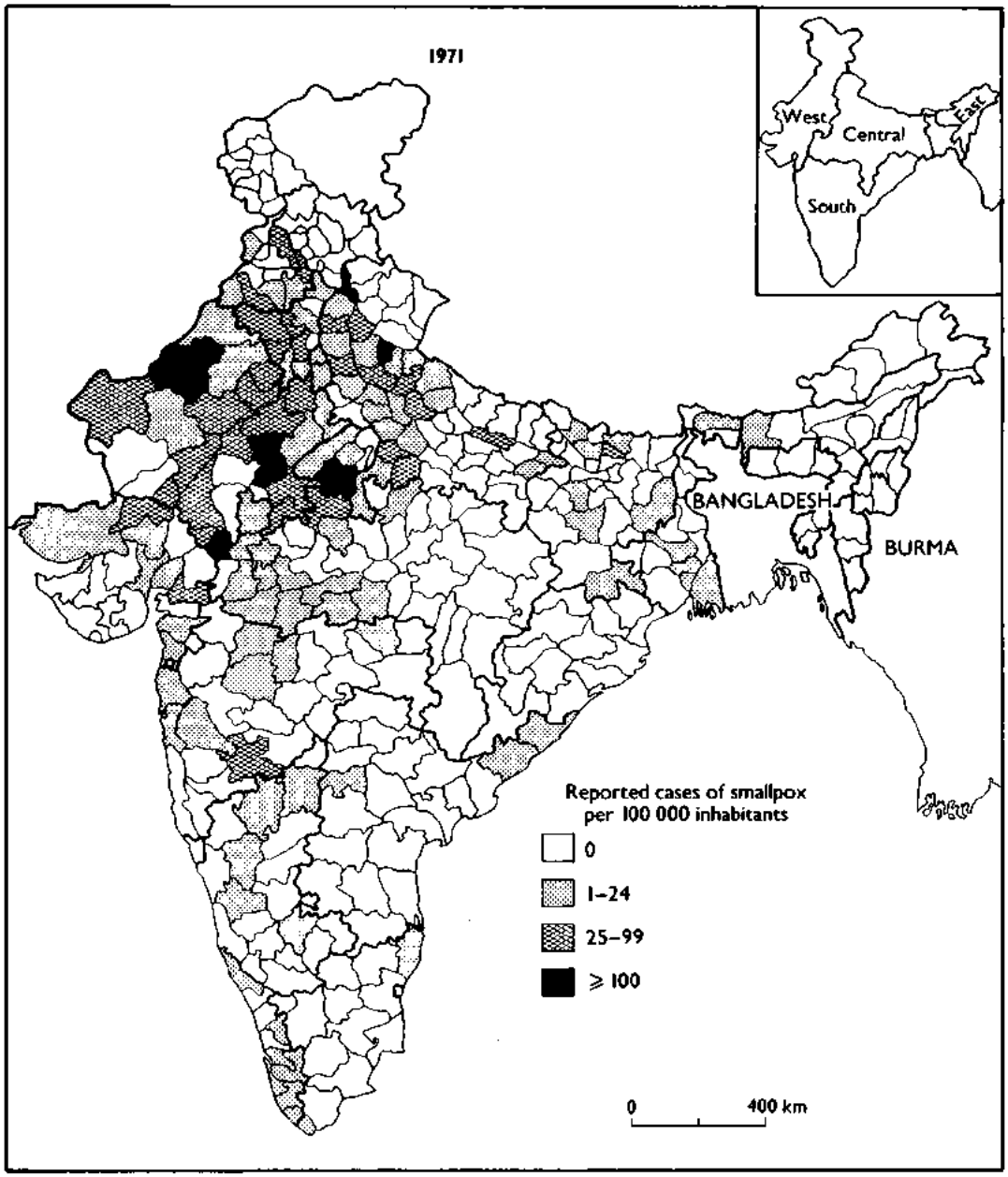


Fig. 15.6. India: number of reported cases of smallpox per 100 000 inhabitants, by district, 1971.

Smallpox eradication activities continued in all states throughout 1971–1973, with varying levels of success. During this period there were developments of particular note in the western states and in Uttar Pradesh, as well as in certain of the areas of low incidence in the south, and an unanticipated setback originating in a Bangladeshi refugee camp in West Bengal. These are described below.

Western India, 1971–1973

It had been hoped that the dramatic success of the surveillance–containment programme in Gujarat might be repeated in the other western states and in Uttar Pradesh, in which epidemics were then beginning. Dr Monnier, assigned to Jaipur, the capital of Rajasthan, and Dr Moukhopad, assigned to Lucknow,

the capital of Uttar Pradesh, provided needed support. Full-time assignments were deemed advisable: in Rajasthan because health and other services were less well developed in this conglomerate of former princely states than in most of India; and in Uttar Pradesh because of its vast population (91 million) and its dismal performance during the mass vaccination campaign.

Rajasthan, besides having a less adequate structure of health services and a less literate population than much of India, was geographically a problem, nearly two-thirds of its area being desert and semi-desert. Roads were few and working conditions demanding. The population of 26.5 million was principally settled in 151 towns and 33 305 villages, but there were nomads as well. Three state teams were created which were directed, respectively, by the Deputy Director for Communicable Diseases, Dr M. L. Aggarwal; his deputy, Dr D. K. Jagdev; and Dr Monnier. Each was assigned a paramedical assistant. Vehicles were made available sporadically for the state officials but Dr Monnier used his private car for almost a year until it was agreed that WHO would provide him with a vehicle. In addition to training district and local staff in reporting and containment measures during their extensive travels and in specially convened meetings, the teams undertook to detect and contain outbreaks.

As in other countries, the discovery of suspected cases was usually accomplished by questioning village leaders, schoolteachers and their pupils, and people attending weekly markets. In Rajasthan and in many other parts of India, there were two additional methods, unique to India, by which cases could be detected. One consisted in questioning visitors to the Sītalā mata temples. Many villagers came to give thanks to the goddess for recovery from smallpox or to offer homage in the hope that they and their families would be spared a visitation by the goddess. Cases could also be detected in villages when, as was customary in many areas, branches from the neem tree were hung over the front door of a house in which a patient lived. The leaves of the neem were considered to have special cooling properties when applied to the skin of the patient and other, less tangible, properties when hung above the doorway.

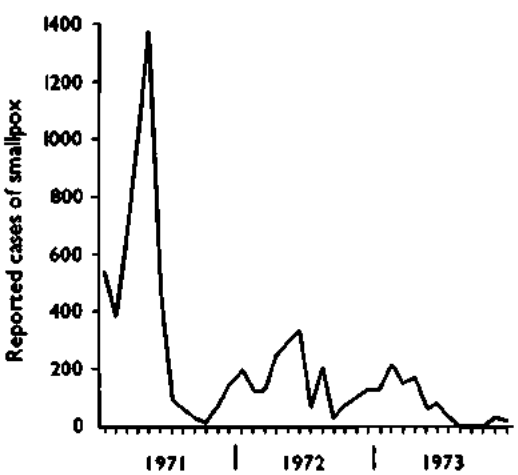


Fig. 15.7. Rajasthan State: number of reported cases of smallpox, by month, 1971–1973.

The programme in Rajasthan made commendable progress. At the beginning of the summer of 1971, the number of reported cases declined steeply, and the incidence remained comparatively low during the spring smallpox season of 1972 (Fig. 15.7). In October, in order to strengthen the programme, other health workers, such as the family planning and malaria eradication programme staff, were directed to report any smallpox cases found during the course of their work. A further decline in incidence occurred in 1973 (Table 15.13), and from August to October 1973 no cases whatsoever were detected. Cases occurred subsequently in Rajasthan, but they originated from importations. The results were impressive and what had been hoped for, although the programme was undoubtedly assisted, as in Gujarat, by a decline in incidence associated with the longer-term fluctuations of smallpox. Nevertheless, little more than 2 years had elapsed between the time the surveillance teams

Table 15.13. Western India: number of reported cases of smallpox, 1971–1973

State or union territory	1971	1972	1973
Chandigarh	0	0	0
Delhi	318	149	168
Gujarat	238	39	9
Haryana	2 635	1 532	188
Himachal Pradesh	11	0	2
Jammu and Kashmir	11	272	941
Punjab	101	139	65
Rajasthan	4 827	1 970	877
Total, western region	8 141	4 101	2 250
Other states and union territories of India	8 049	23 306	85 864
Grand total	16 190	27 407	88 114

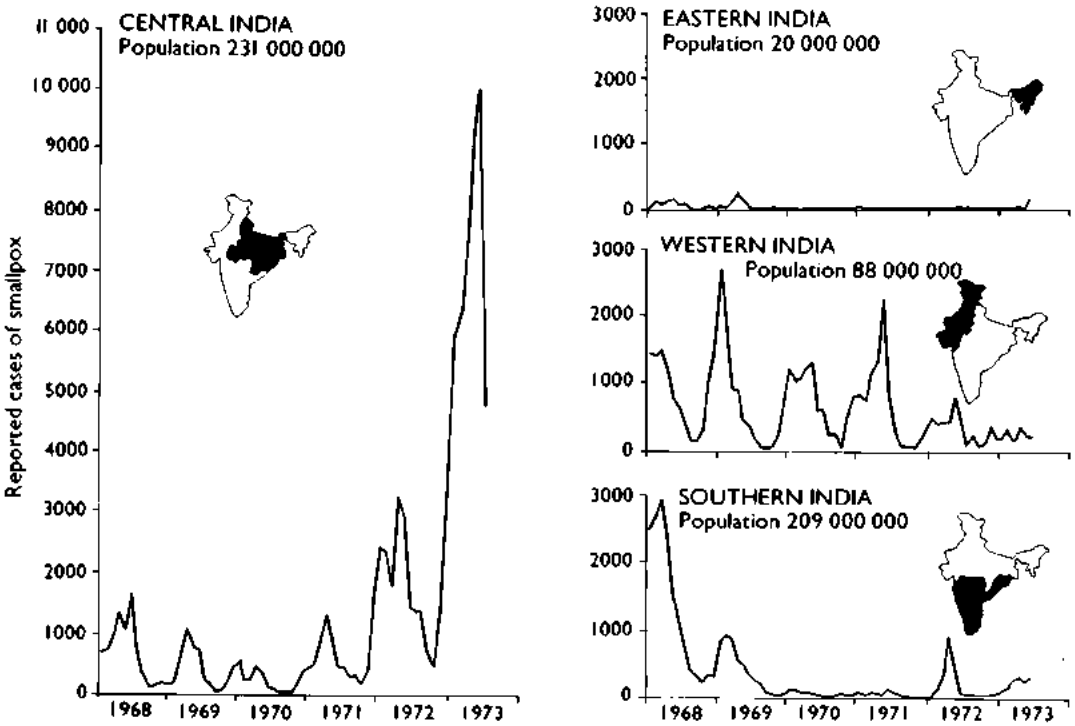


Fig. 15.8. India: number of reported cases of smallpox, by region, by month, 1968–1973. (Population data for 1971 from Basu et al., 1979.)

had begun work and the unprecedented occurrence of 3 months without detectable smallpox.

Dr Singh, through such visits as he could make to the western states near New Delhi, was no less successful in stimulating effective surveillance–containment programmes. The number of cases in the contiguous states of Haryana, Himachal Pradesh and Punjab and in Delhi Municipal Corporation (total population, 32 million) fell somewhat less steeply than in Rajasthan, but by the winter of 1972–1973 fewer than 100 cases were being detected monthly, many of which resulted from importations from the neighbouring state of Uttar Pradesh. By September 1973, transmission had been interrupted throughout this entire area, the only reported cases resulting from importations into New Delhi.

Meanwhile, the programme in Gujarat had progressed so satisfactorily that only 44 outbreaks were detected during the first 6 months of 1971, and none whatsoever from July to the end of October. It seemed impossible that transmission could have been stopped in a state so heavily infected as recently as 1970. Accordingly, Arita was asked to direct a special assessment of the state in November 1971. During a 3-week period, he led a 6-member team which visited 90 towns and villages in high-risk areas of 11 districts. No evidence of smallpox since June of that year could be found. The success reflected, in part, improved case detection and containment of outbreaks, but intensive vaccination undoubtedly also played a role. District surveys in September 1971 revealed that vaccination scars were present in 98–99% of those aged 5–14 years, in 96–99% of those aged 1–4 years and in 66–88% of those aged less than 1 year.

The smallpox eradication programme throughout the western states was progressing everywhere as had been hoped (Fig. 15.8) with a single exception—the northern state of Jammu and Kashmir (population, 4.8 million), which had once been free of smallpox. In the autumn of 1972, the state began reporting increasing numbers of cases. Until October, Jammu and Kashmir had experienced only occasional importations which, according to state reports, had been quickly contained. It had been hoped that by preventing smallpox from becoming re-established in Himachal Pradesh, a geo-

graphical barrier to the northward spread of the epidemic would be created, preventing the disease from reaching Jammu and Kashmir. Dr Singh, working with effective state programme staff, proved successful in maintaining the non-endemic status of Himachal Pradesh. Unfortunately, many travellers to Jammu and Kashmir imported smallpox from infected areas more than 50 kilometres away. Because of the paucity of senior smallpox advisers, assistance had not been provided to state staff in Jammu and Kashmir and the health services had been unable to cope. The failure to strengthen activities in this state was an omission for which the programme would subsequently pay dearly in additional effort.

Uttar Pradesh, 1971–1973

The development of surveillance–containment programmes in the western states proved to be comparatively straightforward, but in the adjacent state of Uttar Pradesh, the experience was entirely different. Uttar Pradesh was India's most populous state (population, 91 million) with a density of 300 persons per square kilometre. Most of the state comprises the Ganges river plain, where population densities were among the highest in India and where transport and communication services were quite well developed. There was an extensive, well-established infrastructure of health services and a large, reasonably well trained health staff. In retrospect, unexpected problems might perhaps have been foreseen because of Uttar Pradesh's poor performance in the mass vaccination campaign, and because it was the last state in India to replace the rotary lancet with the bifurcated needle (1971).

During 1971, Dr Moukhopad and the state programme officer travelled extensively to conduct regional training programmes for all district health officers and their programme staff. However, almost as soon as they were trained in reporting and in surveillance–containment procedures, they were transferred to other districts or assumed other duties. Many who reported substantial numbers of cases of smallpox from their districts were disciplined by the state Director of Health Services by being transferred to hardship posts on the grounds that the presence of cases was tacit evidence that they had not conducted an effective vaccination campaign. Although other states followed this practice, none did so as frequently as Uttar Pradesh and neighbouring states in northern India. Continuing efforts were made by national staff and WHO advisers to persuade state officials that their actions were counter-productive, but with only partial success.

Progress in the programme in Uttar Pradesh was difficult to assess, in part because of the suppression of reports by district officers and in part because of the archaic state and national reporting system. During 1971, the number of cases reported from Uttar Pradesh to the Central Bureau for Health Intelligence never reached 500 per month, and indeed between July and September of that year fewer than 100 cases were notified each month for the entire state. The relevant data, reported to the Central Bureau and to WHO up to 26 October 1971, are shown in Table 15.14 (*Wkly epidem. Rec.*, 1971b). Even if one were to assume that there were 10 times as many cases as had been reported, not only Uttar Pradesh but India as a whole appeared to have very few chains of smallpox infection. On the basis of a growing experience with surveillance–containment programmes, it seemed reasonable to expect that transmission could be interrupted comparatively easily and rapidly. The greatest impediment in assessing the true situation and in deciding how best to deploy resources to achieve this goal was the reporting system.

In November 1971, the government and a new acting director of the Central Bureau for Health Intelligence agreed to modernize the reporting system so that its procedures would resemble those used in other countries. Each primary health centre was directed to notify to the district on Saturday of each week the total number of cases detected that week irrespective of the date of onset. If no cases were reported, a "nil" report was to be submitted. The submission of a nil report was a most important feature. Previously, the absence of a report had been assumed to mean an absence of cases when, in fact, the responsible medical officer may have been negligent in reporting or had decided not to report because there were a great many cases. Officials who had been accustomed to suppressing information through the simple expedient of not submitting a report found it difficult to indulge in deliberate falsification. The districts were asked to ensure that reports from all primary health centres were

Table 15.14. India: number of reported cases of smallpox, by state and union territory and by month, 1971[a]

State or union territory	Population[b] (millions)	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Total
South[c]											
Andhra Pradesh	44.8	50	28	58	29	14	12	0	0	0	191
Goa, Daman and Diu	0.9	0	0	0	0	0	0	0	0	0	0
Kerala	22.0	63	39	10	2	0	0	0	0	0	114
Maharashtra	51.9	1	3	15	8	3	16	24	16	25	111
Mysore[d]	30.2	13	37	34	5	0	36	10	9	1	145
Orissa	22.6	1	1	3	0	4	2	2	0	0	13
Tamil Nadu	42.4	0	0	5	0	0	0	0	0	0	5
East[c]											
Assam	15.1	35	0	0	0	0	0	0	0	0	35
Manipur	1.1	0	0	0	0	0	0	0	..	..	0
Nagaland	0.5	0	0	..	..	..	..	..	..	..	0
North East Frontier Agency[e]	0.5	0	0	0	0	0	0	0	..	..	0
Tripura	1.6	0	0	0	0	0	0	0	0	0	0
West											
Chandigarh	0.3	0	0	0	0	0	0	0	0	0	0
Delhi	4.2	2	7	70	86	89	34	12	8	3	311
Gujarat	27.5	18	79	53	27	20	0	0	0	0	197
Haryana	10.3	139	280	426	270	651	336	141	19	13	2 282
Himachal Pradesh	3.6	0	0	0	0	1	0	2	0	..	3
Jammu and Kashmir	4.8	0	0	0	2	7	0	0	..	..	9
Punjab	13.9	27	19	4	3	10	1	0	0	0	64
Rajasthan	26.5	545	383	917	943	786	482	65	44	8	4 173
Central											
Bihar	58.0	28	33	336	179	109	77	97	..	63	922
Madhya Pradesh	42.9	72	63	37	112	21	53	43	21	2	424
Uttar Pradesh	90.9	275	347	417	405	319	135	69	27	20	2 014
West Bengal	45.6	4	40	102	49	38	18	5	1	1	258
Total		1 273	1 359	2 487	2 120	2 072	1 202	470	145	143	11 271

[a] Data reported to WHO up to 26 October 1971 (*Wkly epid. Rec.*, 1971b). .. = data not recorded.
[b] Population estimates by state are based on United Nations (1985) data for all of India proportionately allocated by state on the basis of the 1971 census.
[c] No cases were reported during this period in the union territories of Andaman and Nicobar Islands, Dadra and Nagar Haveli, Lakshadweep, Pondicherry, and Mizoram, and the state of Meghalaya.
[d] Became the state of Karnataka late in 1973.
[e] Became the union territory of Arunachal Pradesh in 1972.

submitted and to compile all reports then available on the following Tuesday and to send them to the state smallpox eradication programme office. The state, in turn, was made responsible for ensuring that all districts reported and, on each Thursday, for telegraphing a report to the Central Bureau for Health Intelligence and the National Smallpox Eradication Programme office. Many months, and in some states several years, of work were required before the reporting system functioned well but a major obstacle to the achievement of eradication in India had at last been removed.

In November 1971, Uttar Pradesh was the first state to implement the new reporting scheme. By February 1972, the number of districts which had not reported for 3 weeks or more had fallen from 17 to only 5, and by summer, 48 of the 55 districts were submitting reports promptly each week. Whether because of improved reporting or because of an actual increase in incidence, the number of recorded cases rose during the winter of 1971–1972 to between 1200 and 1600 each month (Fig. 15.9)—but still, in a population of 91 million, this was not a great number. Senior staff continued to believe that with sustained support to the surveillance–containment effort, Uttar Pradesh would repeat the experience of the western states. It was not to be. Smallpox eradication staff were diverted to perform cholera vaccinations between September and December 1972, at a time when the containment of smallpox outbreaks was most crucial. Although cholera vaccine had been shown to be of little value, this was the usual and politically acceptable response of the health services when cholera occurred. Explosive outbreaks of smallpox spread across the state; the number of cases increased rapidly during the early months of 1973, reaching a peak in May, when 5000 cases were reported.

Particularly discouraging was the continuing antipathy of state officials to the surveillance–containment strategy. An episode in early April 1973 in the district of Muzaffarnagar vividly illustrated the prevailing attitude. This district, located less than 100 kilometres north of New Delhi, began experiencing outbreaks of smallpox in the autumn of 1972 and, in January, reported 440 cases. This greatly exceeded the number reported that month by any other district of India except 2 districts in West Bengal associated with the Salt Lake Refugee Camp disaster (see later in this chapter). In February 1973, Arita joined Dr Moukhopad in a special investigation of the problem. Active searches at schools and markets soon revealed that although the reported smallpox incidence was high, there were many other undetected and uncontrolled outbreaks occurring throughout the district. With the cooperation of a responsible, energetic district health officer, they decided to mobilize all health staff throughout the district by closing the health centres and training the staff to undertake a 2-week systematic village-by-village search for cases. The health staff responded with enthusiasm and efficiency and soon discovered that cases were occurring in more than half the villages. In all, 641 cases were discovered in February and 1219 in March. Containment measures had scarcely begun, however, when the state Director of Health Services ordered the cessation of all surveillance–containment operations and the immediate vaccination of the entire population of the district. He then warned that when this had been completed the report of any further cases would result in the transfer of the district health officer to the most unpleasant post in the state. It was clear that considerable persuasion of state officials and heroic efforts in the field would be required if Uttar Pradesh was to become free of smallpox. However, the demonstration that it was possible to mobilize effectively the poorly supervised army of health staff offered hope for the future.

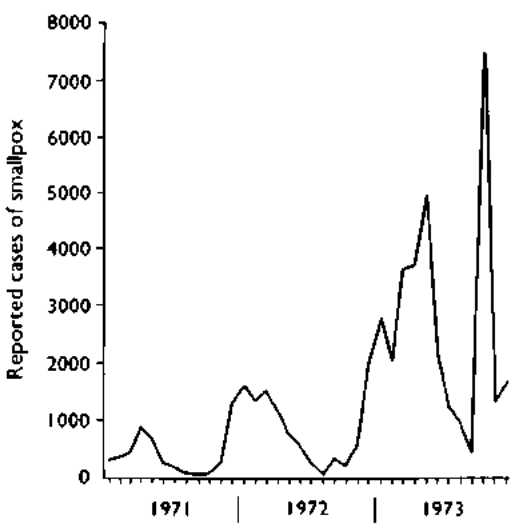


Fig. 15.9. Uttar Pradesh State: number of reported cases of smallpox, by month, 1971–1973.

The southern states, 1971–1973

In the southern states, it had been hoped that the WHO adviser, Dr Zikmund, working with state programme officers might succeed reasonably quickly in developing surveillance–containment activities to the point of interrupting transmission throughout the entire area. Tamil Nadu continued its successful programme and from the beginning of 1971 to the end of 1973 only 11 cases were recorded (Table 15.15), all following well-documented importations. Mysore (renamed Karnataka in 1973) and Andhra Pradesh, the contiguous states to the north, were targets of high priority. Virtually all cases in Andhra Pradesh occurred during the first half of 1971 among generally uncooperative, poorly vaccinated fishermen who migrated seasonally between Andhra Pradesh and Orissa. District health officials, considering them to be temporary residents, had ignored them. Once vaccination and outbreak containment began, transmission quickly stopped. In Mysore, 185 of the 223 cases reported during 1971 were from a single district and these outbreaks were contained by midsummer. Maharashtra was also successful in stopping transmission. In the entire southern area, between October 1971 and January 1972, only 45 cases were detected, all of them occurring in 3 districts. Considering that the southern states accounted for 38% of India's total population, there was reason for optimism about the prospects for the eradication of smallpox in India.

Uncertainty persisted, however, about the situation in the state of Kerala. There, smallpox transmission appeared to have been interrupted in 1967, only 42 cases, presumably importations, having been detected between 1968 and 1970. However, between January and May 1971, 105 cases were

reported, with 1 additional case in September and 2 in November. Kerala's health services, among the best in India, reported that the cases had not occurred in outbreaks as one would expect, but rather were scattered across 7 of its 10 districts. Because the epidemiological pattern of the cases was difficult to explain, Arita joined state officials in a special study in February 1972. Of the reported cases, 70% were found to be in persons over 15 years of age, and of the patients whose vaccination status was known, 102 had previously been vaccinated. Arita and his collaborators examined 35 patients who had recovered, but none had the residual pockmarks typical of smallpox. As it turned out, the state in late 1970 had requested health staff to begin to collect specimens from patients with chickenpox as well as from those with suspected smallpox to confirm with greater certainty that the state was smallpox-free. A state laboratory with little experience in the identification of variola virus had examined the specimens using the gel-precipitation technique and reported that 104 out of 386 tested were either "positive" or "doubtful" for variola virus. Although there was little doubt on the part of physicians about the clinical diagnosis, the virological reports were accepted and the cases duly notified. The team eventually concluded that none of the reported cases was smallpox and the reports were retracted. Except for 4 imported cases in 1974, Kerala was to remain smallpox-free.

The findings in Kerala provided further encouragement but, in February 1972, it suddenly became apparent that there were serious, hitherto unrecognized, problems in Mysore. The discovery of smallpox in Mysore was made by surveillance teams in the neighbouring state of Andhra Pradesh, whose programme was directed by Dr M. C. Appa Rao. There, case detection had improved significantly when, at the end of 1971, a sum of 10 rupees (US$1.33) was awarded by the government for the discovery of a case—the first time in India that such a reward had been offered. The teams detected outbreaks in Hyderabad whose source of infection was a village in Gulbarga District, one of 19 districts of Mysore State. The outbreak was unknown to the Mysore state programme officer. The district (population, 1.7 million) had an extensive network of health facilities, including a large general hospital, 71 health centres and dispensaries, a medical college, and special programmes for the control of malaria, filariasis and tuberculosis and for family planning. It was assumed that if smallpox cases had been present, they would have been quickly detected. State officials, in collaboration with Dr Zikmund, began an immediate investigation. It soon became apparent that not one but numerous outbreaks had occurred, beginning almost 15 months earlier, in December 1970. By the end of March, the investigators had discovered 81 outbreaks and 730 cases. They found that even the staff members of primary health centres who lived in villages with major outbreaks had not reported them; many directors of primary health centres who were notified of cases dismissed them as chickenpox; and, indeed, the District Director of Health and Family Planning, who had been officially informed of smallpox cases as early as September 1971, had suppressed the reports. It was concluded that radical measures would be required to stop the epidemic.

Able leadership was provided by a newly appointed District Medical Officer of Health, Dr Rama Rao; health staff were transferred from other districts; and all health and family planning staff in Gulbarga District were mobilized to undertake repeated house-to-house searches for cases throughout the district. When outbreaks were discovered, they were promptly contained. New outbreaks rapidly decreased in number, from 34 in April to 12 in May and 4 in June. To counter the tendency to conceal cases, a reward of 25 rupees (US$3.33) was offered to anyone who reported a case of smallpox.

Table 15.15. Southern India: number of reported cases of smallpox, 1971–1973[a]

State or union territory	1971	1972	1973
Andhra Pradesh	214	405	1 295
Dadra and Nagar Haveli	0	0	1
Kerala	0	0	0
Maharashtra	160	215	158
Mysore[b]	223	1 299	6
Orissa	16	5	1 276
Tamil Nadu	7	1	3
Total	620	1 925	2 739
Other states and union territories of India	15 570	25 482	85 375
Grand total	16 190	27 407	88 114

[a] No cases were reported during this period from the union territories of the Andaman and Nicobar Islands, Goa, Daman and Diu, Lakshadweep, and Pondicherry.
[b] Became the state of Karnataka late in 1973.

Chickenpox—a Problem in Surveillance in Kerala

Cases of and deaths from severe chickenpox proved the most difficult in differential diagnosis. The most problematic cases were those in adults. Among residents of the southern state of Kerala (population, 24 million), as well as among migrants from that state, cases of chickenpox in adults occurred with unusual frequency, and this resulted in a number of erroneous reports and special investigations. In the process of confirming that transmission had been interrupted in India, a special study was conducted in Kerala to ascertain that the deaths attributed to chickenpox had been correctly diagnosed (White, 1978).

Age Distribution of Deaths Due to Chickenpox, January 1975–March 1976

Age group (years)	*Males*	*Females*	*Total*	*Prevalence per 100 000 of cases of chickenpox*[a]
0–4	6	3	9	64
5–9	2	1	3	102
10–19	4	3	7	87
20–29	1	3	4	59
30–39	14	3	17	56
40–49	34	1	35	69
50–59	34	5	39	48
60–69	31	14	45	31
⩾70	74	27	101	36
Total	200	60	260	71

[a] Based on a special search in April 1976 in 11 primary health centres.

Of 260 persons who died of chickenpox over a 15-month period, 241 were 20 years of age and older. For many, the immediate cause of death was attributed to "old age" or a chronic or unrelated acute illness, although chickenpox may have been cited as a contributory factor.

It was suggested that the frequency of adult cases related to the dispersed population in Kerala and, until recently, the difficulty of travelling from one village to another. Thus, it was reasoned, many were not exposed to chickenpox until they were adults. The hypothesis was attractive, but other factors must have been involved because adult chickenpox was not such a problem in other, even more isolated, areas of Africa and Asia.

However, cases spread from Gulbarga to 5 other districts in Mysore, to 2 districts in Andhra Pradesh and to at least 1 district in Maharashtra. More than 1400 cases in all were traced to this single district. Although the outbreaks were largely contained in a period of 2 months, fully 6 months elapsed before transmission finally ceased. Most surprising to senior Indian and WHO staff alike were the numbers of health staff who could be mobilized, the rapidity with which a search programme could be organized, and the responsiveness of staff in executing a well-conceived plan. This experience was subsequently replicated in Muzaffarnagar District, Uttar Pradesh (see previous section) and, in May 1973, throughout Orissa State. It ultimately led to the plan to undertake nation-wide searches for smallpox cases—the essential strategic component of the campaign beginning in the autumn of 1973.

Although transmission was successfully interrupted in Mysore by September 1972, Hyderabad, the capital of Andhra Pradesh, had by then been reinfected; from there the disease spread to 8 other districts. Dr Appa Rao, who was responsible for other programmes in addition to smallpox eradication, was unable to devote sufficient time to the programme and smallpox continued to spread, albeit slowly. Smallpox was reasonably well contained, with the help of Dr Zikmund, until January 1973, when he was forced to leave for Orissa because of outbreaks there

resulting from importations from the Salt Lake Refugee Camp. Smallpox continued to spread in Andhra Pradesh. Between January and June 1973, 924 cases occurred. In view of the size of the population (47 million), the number of cases was not large but, clearly, transmission in Andhra Pradesh and the southern states was not being interrupted as quickly or as easily as had been hoped. The potential for epidemic spread remained, as the Gulbarga experience had shown. The movement of smallpox was too rapid and effective to be contained by the few epidemiologists available.

West Bengal and the Salt Lake Refugee Camp, 1971

The densely populated state of West Bengal (population, 46 million), with its crowded capital city of Calcutta (population, 7 million), was a demographic centre of vital importance to smallpox eradication in the eastern states of India. In West Bengal, progress in the control of smallpox appeared to be satisfactory—until December 1971. The number of recorded cases had diminished to only 374 in 1970 and to 217 in 1971, the lowest totals ever reported. The Eastern Province of Pakistan (later Bangladesh) on its eastern border, predominantly Muslim but also Bengali-speaking, had detected its last case in August 1970 (see Chapter 16). Thus, importations of smallpox by travellers who frequently crossed the border were not a threat. However, civil war began in March 1971 in East Pakistan, and during that year an estimated 10 million refugees fled across the border into India. Numerous refugee camps were set up, primarily in West Bengal, Madhya Pradesh and Assam. It was feared that if smallpox were introduced into the camps, devastating epidemics would rapidly develop. On the orders of the National Smallpox Eradication Programme staff, all refugees entering the camps were examined for the presence of smallpox, but no cases were found. As a preventive measure, state officials were requested to ensure that all persons entering the camps were vaccinated. Indian national staff and WHO advisers visited and confirmed that this procedure had been followed in a number of camps, but not in West Bengal, where the state authorities refused to permit national intervention. The largest refugee camp, the Salt Lake Camp near Calcutta, sheltered an estimated 200 000–300 000 persons, and there an international private voluntary organization had been given responsibility for providing health services. For reasons unknown, no vaccination campaign was conducted.

Smallpox was probably introduced into the Salt Lake Camp in November. Many cases were hospitalized within the camp but were diagnosed as chickenpox. The diagnosis of probable smallpox was finally made on 19 January 1972 by an epidemiologist in the USA while viewing a television news documentary made in the camp. The report was relayed rapidly from Atlanta to Geneva to New Delhi. The Director of Health Services of West Bengal categorically denied there were cases, but Dr S. N. Ray, from the National Programme office, flew to Calcutta and, on visiting the camp, found an extensive outbreak. A vaccination programme was begun, but it was too late. On 16 December 1971, one month earlier, the independence of Bangladesh had been proclaimed. By 20 January 1972, an estimated 50 000 refugees had already departed for Bangladesh. The epidemic spread from the camp through West Bengal and from there to the neighbouring states of Orissa and Bihar. West Bengal, which had detected only 217 cases in 1971, reported 4753 in 1972; Bihar reported 1307 cases in 1971 and 4153 in 1972.

The number of cases that occurred in the camp can never be known, but as from 22 January, infected persons among the refugees remaining in the camp were admitted to the Calcutta Infectious Diseases Hospital; admissions continued until the end of February. During this period, the hospital admitted 764 patients, of whom 48% died (Guha Mazumder & Chakraborty, 1973).

West Bengal, which had been comparatively free of smallpox in 1971, became a major epidemic focus in 1972 (Fig. 15.10) and Bangladesh was again reinfected (see Chapter 16).

The beginning of the "final phase" of the Intensified Smallpox Eradication Programme, November 1972

By the autumn of 1972, global progress in the Intensified Programme was most encouraging. Only 3 endemic countries remained in the whole of Africa—Ethiopia, Botswana and the Sudan—and in the latter two interruption of transmission appeared imminent. Both South America and Indonesia were smallpox-

free and Afghanistan was almost so. Bangladesh had been reinfected but it had re-established its national programme and Pakistan's programme had been extended to the entire country. India was reporting increasing numbers of cases as epidemic smallpox began moving across the Ganges plain from the west and from Calcutta in the east. However, the extent of the infected areas in India, as well as in other Asian countries, had diminished significantly (Fig. 15.11).

With endemic smallpox so limited geographically and some form of surveillance operating in all areas, it seemed to WHO propitious to encourage a more concentrated effort in the remaining infected areas: the "final phase" of the Intensified Programme. The proposed target was ambitious—to interrupt smallpox transmission during the following 2 smallpox seasons, a period of about 18 months. To encourage the renewed effort, special seminars were convened in

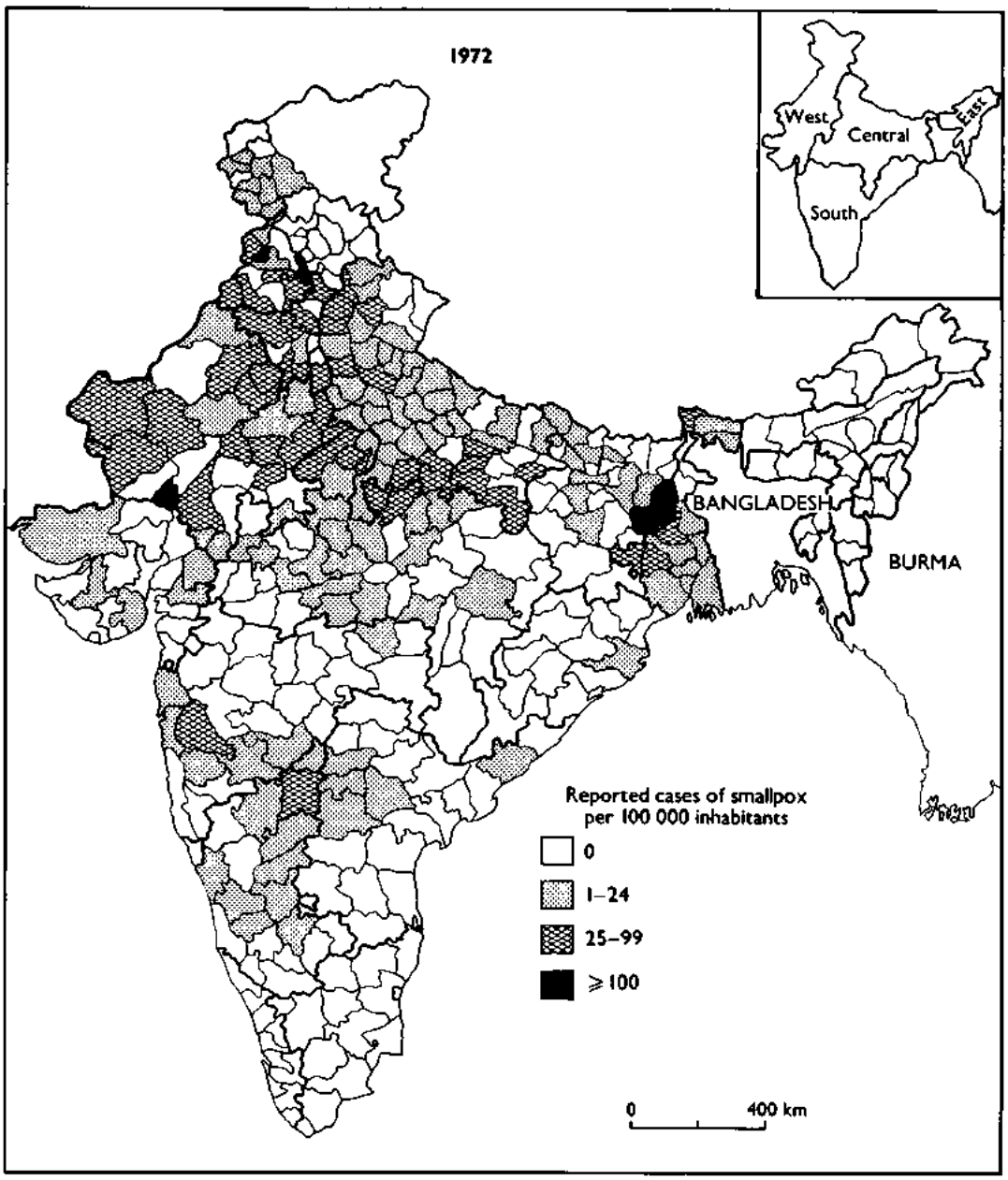


Fig. 15.10. India: number of reported cases of smallpox per 100 000 inhabitants, by district, 1972.

September–November in Addis Abeba (mainly for staff in Ethiopia and the Sudan); in Karachi (principally for staff in Afghanistan and Pakistan); and in New Delhi (for staff in Bangladesh, Bhutan, India and Nepal).

In India, despite the success of surveillance–containment measures in southern and western states, many state health officials still persisted in their belief that 100% vaccination was the only way to achieve eradication. With officials from all over India attending the seminar, attention was focused explicitly on the surveillance–containment strategy. The success in Indonesia was a helpful stimulus in encouraging a change in direction, as is illustrated in the following extract from Henderson's opening address:

"Two years ago, in December 1970, a seminar on smallpox eradication was held in this very room. I said at that time that the question was repeatedly asked as to how such major changes [in the smallpox eradication programme] could occur so rapidly when, for years, many endemic countries had been conducting mass vaccination programmes with only limited success. The principal difference between present and past efforts is one component—surveillance. In every country where a concerted effort has been made to investigate promptly and to contain *every* outbreak, smallpox transmission has been interrupted within two years or less. Many of you will recall that at that Seminar the director of the Indonesian programme presented a provocative paper which stated 'a proper surveillance–containment action brought smallpox under control in a short period,

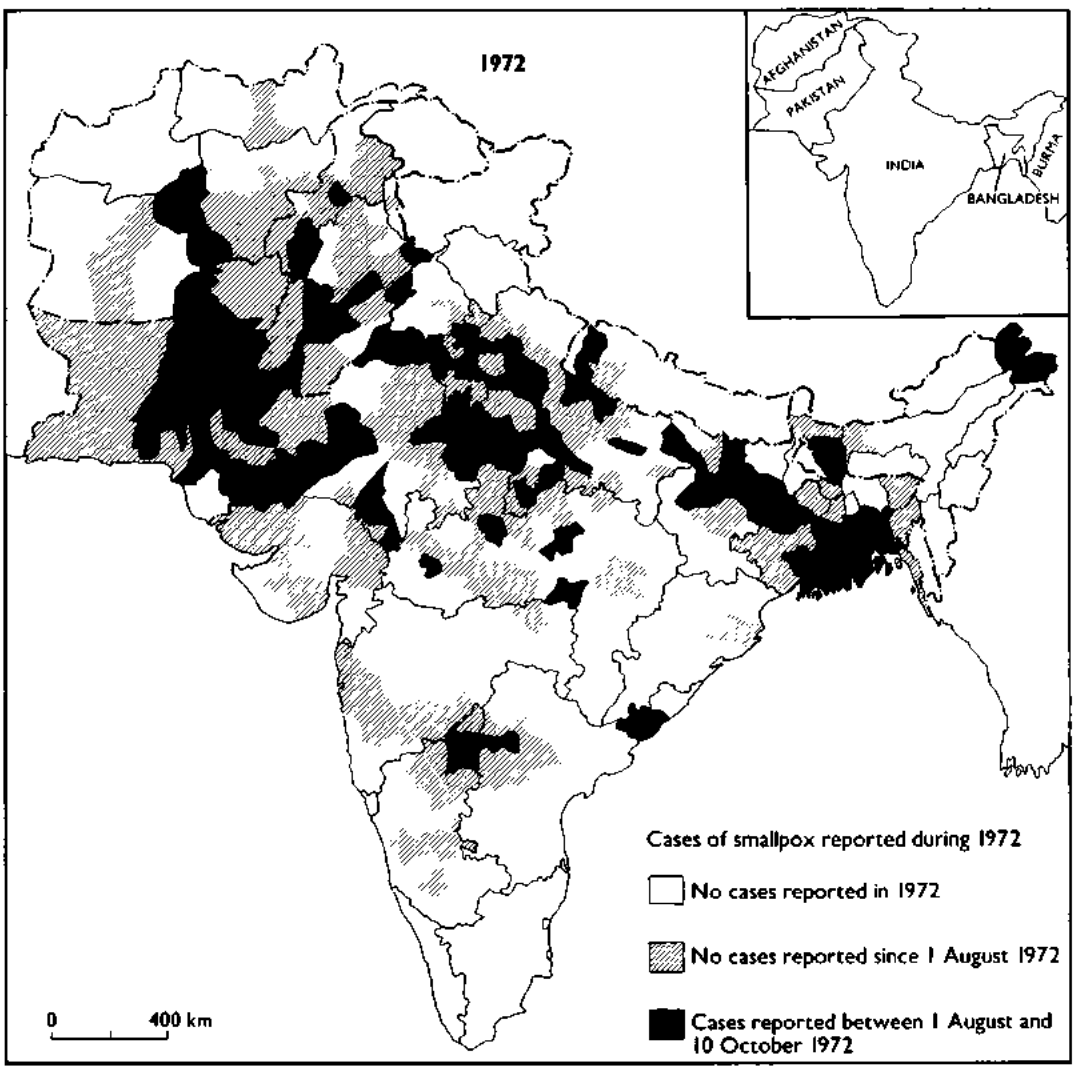


Fig. 15.11. Indian subcontinent and adjacent countries: areas reporting cases of smallpox during 1972 (as of 10 October).

while on the contrary, routine vaccination and mass vaccination campaigns had little effect in interrupting smallpox transmission'. That year, Indonesia reported 10 000 cases of smallpox, only 20% fewer cases than in India. Many at that Seminar took violent exception to the Indonesian director's contention that all available resources should be diverted to surveillance even at the expense of a vaccination campaign. Who was right? I would ask you to note that the number of cases in Indonesia decreased from 10 000 in 1970 to 2000 in 1971 and to 34 this year. Despite a continuing active search for cases, none have been found in all of Indonesia for over eight months."

State health authorities in India had argued that there were not enough health staff. However, it was noted that, even in countries

Plate 15.5. Refugees from East Pakistan, many infected with smallpox, leave the Salt Lake Camp near Calcutta in December 1971 to return to their newly independent country, Bangladesh.

with less well developed health infrastructures, such as Ethiopia, only 80 workers were employed (1 for every 300 000 persons) and in Afghanistan the corresponding ratio was 1 for every 100 000 persons. In India, 1 smallpox vaccinator was available for every 8000–20 000 persons.

The need for surveillance was echoed in the address by the Indian Minister for Health and Family Planning and by Dr P. Diesh, the Additional Director-General of Health Services, who concluded the seminar with the statement: "History tells us that whoever rules the Indo-Gangetic plain rules the country. The battle of smallpox will be fought in the Indo-Gangetic plain, where 70% of the cases are reported now." And this indeed was where the major battle was fought over the following 3 years.

The seminar report concluded with a number of recommendations which stressed surveillance:

1. It is essential to delineate smallpox endemic and non-endemic areas within a state or country. The endemic areas should receive highest priority and the major part of the resources at present available. In the non-endemic areas, an active search for cases should be planned and implemented to ensure their smallpox-free status. Any suspected cases should be dealt with as a national public health emergency.

2. In states where surveillance teams are not yet in existence, state teams should be created by 1 December 1972.

3. The investigation of all outbreaks by the state programme officer or at least by state surveillance teams is essential.

Other recommendations emphasized the importance of containment and the need to trace the source of outbreaks. It was also noted that "the newly introduced reporting system in India should be improved as rapidly as possible". The new system was that previously described, in which primary health centres, districts and states reported weekly all cases of smallpox detected during a given week or reported "nil" if no cases were found.

The central programme office was further strengthened in the autumn of 1972, with the appointment of a senior public health officer to head the programme, Dr R. N. Basu, Assistant Director-General of Health Services (Smallpox), who continued in this position until the conclusion of operations. Dr Basu, who held a more senior rank than Dr Singh, carried greater weight with national and state officials. Dr Diesh, who was effectively second in command to the Director-General of Health Services in the Ministry, also took a special interest in the programme and made a number of visits to the state capitals to meet health ministers and directors of health services in order to encourage greater activity. Visits by an official of this rank were uncommon and implicitly indicated that the government accorded high priority to the smallpox eradication programme. Meanwhile, working relationships between WHO staff and Indian national and state staff had gradually become less formal. Arrangements for WHO staff from the regional office to travel to the field and for state-assigned staff to travel from state to state had become a simple matter of discussion and verbal agreement. This was in marked contrast to the earlier formal relationships which required that, before each trip, a written request should be submitted by the WHO Regional Director to the Ministry of Health and that this request should be considered within the Ministry and eventually a formal reply prepared—a process that often took weeks. With each adviser in possession of a vehicle purchased by WHO and an agreement by WHO to defray all travel costs, a further obstacle to the execution of the programme was removed.

1974

Plate 15.6. Rabinder Nath Basu (b. 1928), Assistant Director-General of Health Services, was appointed to direct the National Smallpox Eradication Programme in the autumn of 1972 and continued in this capacity until after the certification of eradication in 1977. He subsequently directed the development of India's Expanded Programme on Immunization and later became the Director of the National Institute of Communicable Diseases.

7 JEZEK

Plate 15.7. Outbreaks of smallpox occurred among poorly vaccinated pavement dwellers in crowded urban areas. The discovery and containment of such outbreaks were a continuing problem throughout the course of the Intensified Programme.

At the November seminar, goals were fixed in terms of geographical areas within which it was hoped endemic smallpox could be contained by the end of March 1973. For India, it was agreed that by that date the objective would be to eliminate endemic smallpox from all areas except the state of Bihar and 49 districts comprising parts of Uttar Pradesh, Madhya Pradesh and West Bengal.

As early as the end of December 1972, it was evident that the problems once again were greater than had been anticipated. As has been mentioned earlier, major epidemics were discovered in the previously smallpox-free state of Jammu and Kashmir. In Bihar State, health workers went on strike, bringing all work to a standstill. In Uttar Pradesh, then the principal focus of smallpox, eradication staff had been diverted to a cholera vaccination campaign. The new reporting system was an improvement over the old one but, even so, half or more of the states and union territories were consistently up to 5 weeks late in reporting cases.

During 1972, 27 407 cases of smallpox were reported from India, an increase of 69% over the 16 190 cases reported the year before. More complete notification undoubtedly accounted for some of the increase but there was no way of measuring the magnitude. In January 1973, predictions as to the expected incidence of smallpox in 1973 were made by WHO Headquarters staff, in consultation with national staff, on the premise that such predictions served to gauge familiarity with the problems in each area, the rate of progress being made or anticipated and the understanding of the epidemiological situation. It was forecast that 30 700 cases would occur throughout the world, of which 17 000 would be in India. It soon became evident that neither WHO nor Indian staff had comprehended the magnitude of India's smallpox problem.

By the end of March 1973, India had recorded 14 376 cases, of which 29% were outside the established target area. Not only were serious problems present in Bihar, Uttar Pradesh, and Jammu and Kashmir, but it had also become apparent that West Bengal had not done well in controlling the epidemic which had spread from the Salt Lake Camp area. By the end of February, 19 cases imported from Calcutta were detected in Orissa and 30 in Bihar. The estimate of the total number of cases in India projected for 1973 was revised upwards from 17 000 to 35 000

and then to 60 000, a figure which would represent the highest number of cases since 1967. Although reporting had undoubtedly improved, smallpox was far more extensive than had been expected; many still did not subscribe to the new strategy of surveillance and containment. During the spring of 1973, smallpox incidence continued to rise and by the end of June, 49 478 cases had been reported, of which 45 697 (92%) were from the 4 contiguous states in or immediately adjacent to the Gangetic plain—Bihar, Madhya Pradesh, Uttar Pradesh and West Bengal. The total number of cases was almost 3 times greater than the number recorded during the same period in 1972. Comparisons with trends in Pakistan and Bangladesh (*Wkly epidem. rec.*, 1973b) portrayed the unfavourable situation in India (Fig. 15.12).

India was then one of only 4 countries in the world with endemic smallpox, and it accounted for nearly 60% of the world's cases. Politicians and senior health officials alike had become increasingly concerned and had taken a greater interest in the programme. The Twenty-sixth World Health Assembly in May 1973 provided an added stimulus.

During discussions in the Health Assembly regarding the smallpox eradication programme, the delegate from Malaysia bluntly assessed the situation. His observations were summarized as follows (World Health Organization, 1973b):

"... an alarming development in recent months had been that serious smallpox epidemics were raging in two of the endemic countries, despite the fact that WHO was now entering the seventh year of its intensified smallpox eradication programme. Among the reasons for the setback, as given in the *Weekly Epidemiological Record* ... were: lack of staff; inadequately developed surveillance programmes; periodic diversion of smallpox staff to other programmes; delayed and incomplete reporting; and inadequate containment measures. Lack of staff should not be an insurmountable problem; it could be overcome by improved deployment of staff and crash recruitment and training programmes. Nor should it be too difficult to organize and develop surveillance programmes. In view of the vital importance of smallpox eradication, any diverting of staff to other programmes would be premature and ill-advised, and inadequate reporting and containment measures indicated a lack of appreciation of the urgency of the problem. He did not wish to criticize any individual country, but he hoped that the points he had raised would be taken in a constructive spirit.

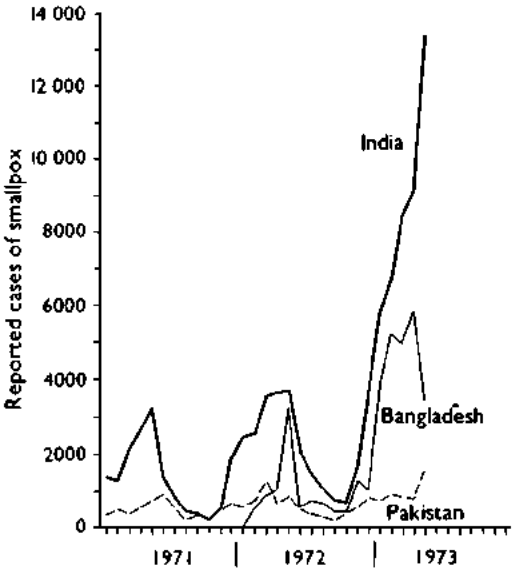


Fig. 15.12. Bangladesh, India and Pakistan: number of reported cases of smallpox, by month, 1971–1973 (as of 19 June 1973).

"WHO had declared that it was willing to send emergency aid on request ... to any country facing problems in smallpox eradication. He wondered whether the countries now suffering from outbreaks had taken full advantage of that offer ..."

In the World Health Assembly, criticism such as this of another country's health programme was unusual; to India's Director-General of Health Services, it was acutely embarrassing. He returned to India determined to strengthen the programme.

Endemic smallpox in India remained comparatively limited geographically (Fig. 15.13) although the number of cases was large, and it appeared that an intensified programme would require a special mobilization of resources in only a few states of India. With the season of diminished transmission immediately ahead, it was decided to initiate an "epidemic of activity" preceding the usual season of epidemic smallpox.

The Intensified Programme in India, June–December 1973

At the end of June 1973, WHO staff from Headquarters and the Regional Office for South-East Asia held meetings with Indian national and state health personnel to devise a new campaign plan whose strategy would be to detect and contain the comparatively

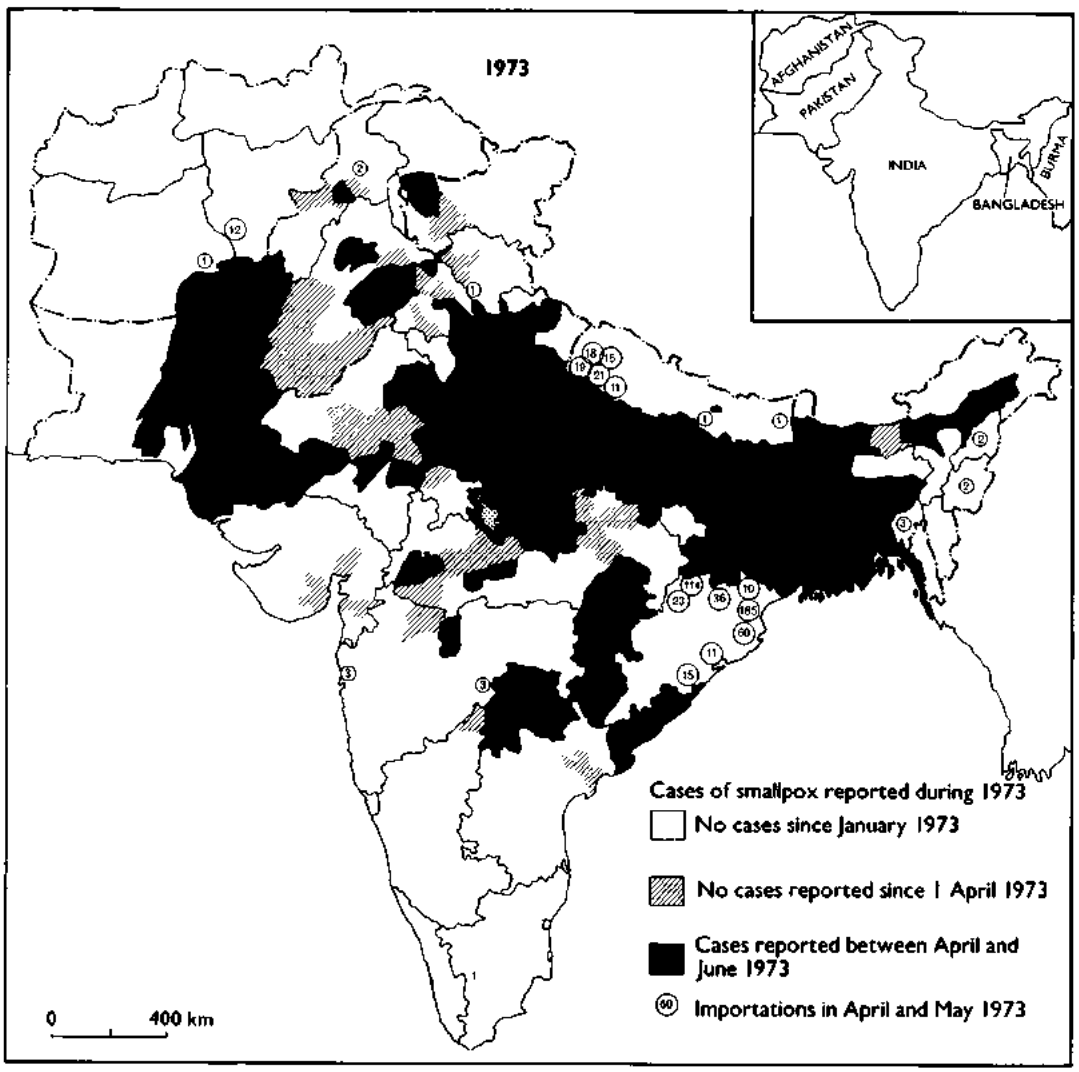


Fig. 15.13. Indian subcontinent and adjacent countries: areas reporting cases of smallpox during 1973 (as of 19 June).

few outbreaks expected to occur during the autumn months of seasonally low incidence. If most of these could be contained by December, it was expected that the remaining foci could also be contained by state and district surveillance teams during the January–June period.

The most highly infected states were Bihar, Uttar Pradesh and West Bengal. There, the deployment of an epidemiologist-adviser and a few surveillance teams for motivating local staff to report cases and to contain outbreaks had clearly failed. A different approach was required. The early detection of cases was of the greatest importance. Once cases were found, a comparatively small number of containment teams could deal with the outbreaks. Everyone had been impressed by the experiences in Gulbarga District (Mysore) and Muzaffarnagar District (Uttar Pradesh), in which it had proved quite simple to plan and execute a village-by-village programme of case detection which could reach all parts of a district within 1–2 weeks. It was reasoned that if a systematic search of this type could be conducted throughout entire states, in combination with an effective containment programme, it should be possible to contain smallpox quickly. To execute such a search in a state, in a group of states or in the whole of India posed problems of organization and motivation of an entirely

different magnitude from those involved in carrying out the operation in a single district. However, it was apparent that throughout the length and breadth of India a large complement of generally well-trained health staff existed—albeit often poorly supervised and supported. It seemed plausible that an increased number of senior smallpox eradication programme supervisors, following a carefully designed plan, could harness this considerable resource for a concerted effort over a period of a few months. This was the basic strategy decided on, and thus began what was to become one of the most ambitious and intensive national health programmes yet undertaken. Eventually, it would involve more than 130 000 staff who, within a 2-week period, could visit more than 90% of the 120 million households in India.

The principal problem area comprised the states of Bihar, Madhya Pradesh, Uttar Pradesh and West Bengal. Their combined population amounted to 249 million, or about 42% of the entire population of India. It was planned to assign a senior Indian epidemiologist and a counterpart WHO epidemiologist-adviser to assist each state smallpox eradication programme officer in these 4 states. An additional WHO epidemiologist would continue to work in the neighbouring state of Rajasthan, in which transmission appeared to have been interrupted but which was experiencing many importations. A sixth WHO epidemiologist would be based in Orissa State to assist in the development of search programmes and the investigation of outbreaks in the low-incidence states and union territories geographically close to the 4 highly infected states. He would also assist with any problems in a third group of states which were thought to have interrupted transmission or were expected to do so by September—the smallpox-free group (Fig. 15.14). Additional transport, supplies and equipment were made available by WHO to supplement the already considerable resources deployed by India.

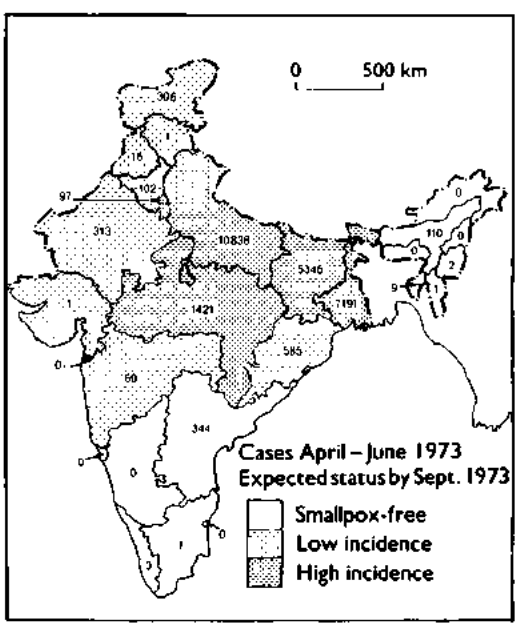
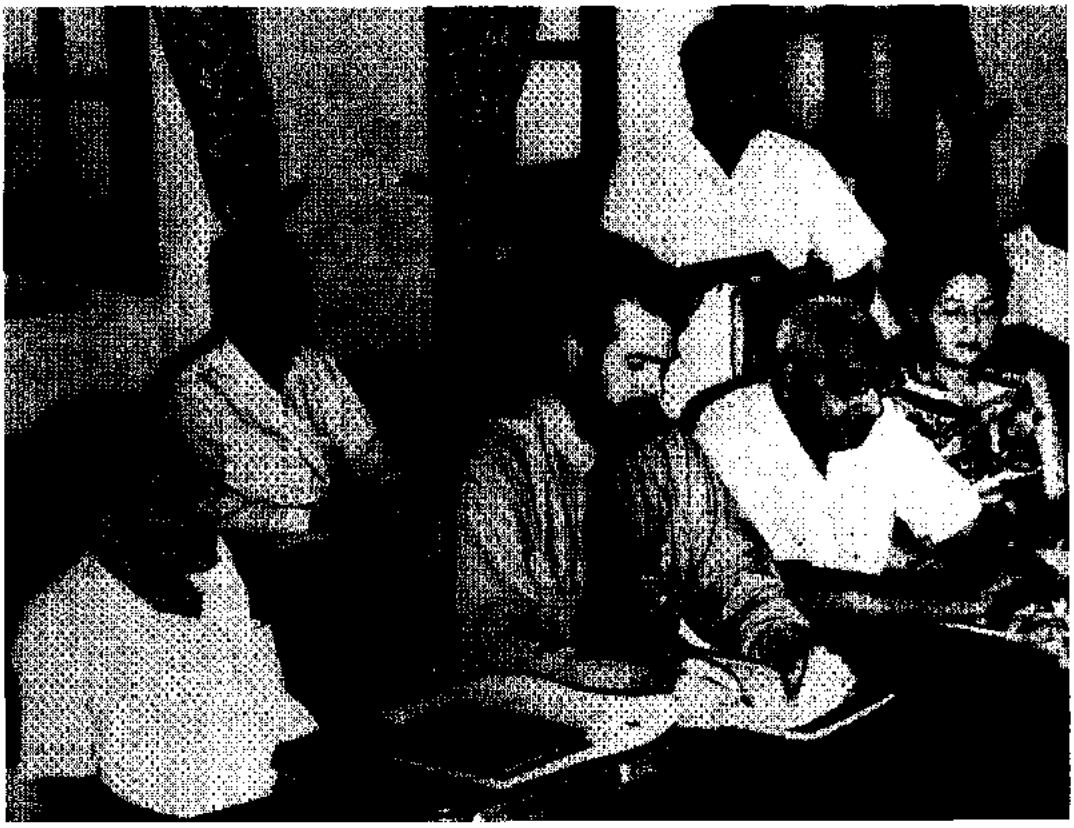


Fig. 15.14. India: autumn campaign of 1973. Number of reported cases of smallpox by April – June 1973 and the expected status of smallpox incidence, by state, in September 1973.

For the 4 highly endemic states, a 3-phase programme was formulated. Phase One, planned for the late summer of 1973, would consist of an active search for outbreaks in municipal areas. It was hoped by this search to find and eliminate urban foci, which often served to sustain smallpox transmission through the summer monsoon season. Because there was insufficient time for preparation, the first phase achieved little except to bring the smallpox eradication activities of most of the autonomous municipal corporations under the supervision of the state smallpox eradication programme office. Phase Two of the programme, from September to December 1973, would consist of statewide, week-long, village-by-village searches on 3 separate occasions approximately a month apart. Two searches would be conducted in the states with a low incidence, and at least 1 search in the states believed to be smallpox-free. Other health personnel and family-planning workers would be utilized to supplement the work of the smallpox eradication staff. The nature of Phase Three, commencing in January 1974, would depend on the status of smallpox at that time; it was expected that it would consist primarily of a search for cases by surveillance teams and the containment of a few remaining outbreaks.

The government of India and WHO agreed to increase the number of senior supervisory staff for this effort. The government provided an additional senior Indian epidemiologist for each of the 4 priority states. It assigned to the programme Dr M. I. D. Sharma, then the Director of the National Institute of Communicable Diseases; two of his epidemiologists, Dr C. K. Rao and Dr R. R. Arora; and the Assistant



BY COURTESY OF R.S. AGARWALA

Plate 15.8. State review meeting in Lucknow, Uttar Pradesh, in 1975. *Seated, left to right*: M. C. Chaturvedi, Additional Director of Medical and Health Services of Uttar Pradesh; C. K. Rao, member of the Central Appraisal Team; J. M. McGinnis, WHO consultant from the USA; M. I. D. Sharma, Commissioner of Rural Health for India; and N. C. Grasset, smallpox adviser from the WHO Regional Office for South-East Asia. *Standing*: M. Dutta, member of the Central Appraisal Team.

Director-General for Cholera, Dr Mahendra Dutta. With Dr Basu and Dr Singh of the National Smallpox Eradication Programme, and Dr S. N. Ray, who was responsible for vaccine production, they constituted the Indian component of a group officially termed the "Central Appraisal Team". The WHO component consisted of the intercountry team (formally, the Smallpox Eradication and Epidemiological Advisory Team), Dr Grasset and Ježek, who were joined that summer by Dr William Foege, who had formerly worked in Nigeria and then at the Communicable Disease Center (later called the Centers for Disease Control) in Atlanta, GA, USA, in directing the smallpox eradication effort in western Africa. In January 1974, Dr Lawrence Brilliant, a new member of the WHO smallpox eradication programme staff, became part of the team.

Beginning in June 1973, the group held frequent meetings, preparing, reviewing, and revising drafts of a "Model Operational Guide for Endemic States" and a "Model Operational Guide for Non-endemic States". To implement the programme in the field, 26 special teams were created. Half the teams were headed by Indian epidemiologists recruited by the government from Indian institutes and universities or brought back from retirement. The other half were headed by epidemiologists of other nationalities recruited by WHO. Twenty-two teams were assigned to the high-incidence states (10 to Uttar Pradesh, 2 to West Bengal, 5 to Bihar and 5 to Madhya Pradesh); 2 teams worked in the eastern states; and the remaining 2 in the smallpox-free and low-incidence states in the south.

Eventually, a total of 230 epidemiologists from 31 countries and a comparable number

of Indian epidemiologists would head such teams for periods of 3–24 months each. As many as 90 epidemiologists would be participating at any one time. Each epidemiologist was given 5 days' training before going to the field. Particularly useful for this purpose was a series of slides prepared by WHO illustrating clinical smallpox and 2 case-history studies, one of which dealt with the day-by-day management and investigation of a smallpox outbreak and the other with the management of a district smallpox eradication programme. (The latter eventually found its way into the syllabus of the Harvard School of Business Administration.)

As the autumn campaign began, there were only 26 epidemiologists in the field (Table 15.16). Each epidemiologist in the high-incidence states worked in a zone covering an average of 5–6 districts (approximately 10 million people) and had as his counterpart the division and/or district health officer responsible for the area. The special teams conducted training sessions for district and local staff to explain and organize the searches. In addition, they supervised the implementation and evaluation of surveillance activities and verified the diagnosis when cases were reported. When smallpox was detected, they organized outbreak containment and identified the source of infection.

Additional vehicles were essential and these were quickly obtained through the purchase by WHO of Jeeps manufactured in India. For WHO, this was a departure from a long-standing policy that the country itself should purchase locally produced equipment and supplies. Prompt delivery of the vehicles would have been impossible if traditional procedures had been followed—i.e., the purchase of Indian-made Jeeps by the government or the purchase of foreign-made vehicles by WHO. To have manoeuvred such a purchase through the complex Indian bureaucracy, even with the highest level of government support, would have taken anything up to a year; the delivery of vehicles from foreign sources was even more protracted at that time. The Indian-made Jeeps, although more susceptible to mechanical failure, were simpler in design and easier to repair. A most important consideration was that spare parts were widely available and there were many mechanics who were familiar with the vehicle. On balance, the Indian Jeeps proved more utilitarian than did imported vehicles.

Each of the epidemiologists was assigned a driver and a paramedical assistant and given a monetary advance (an imprest account) to be used, as necessary, for petrol and vehicle repair, travel allowances and supplies. The funds were accounted for at regular intervals before further advances were made. The disbursement of funds for the discretionary use of the field epidemiologists was also a departure from customary administrative practice, but it was one of the most important steps in facilitating the execution of the programme.

The strategy of the search programme and of the surveillance-containment activities was explained in detail at state-level meetings presided over by state officials and attended by senior officials of the national government and WHO, as well as by state and divisional and/or district health officers. These discussions were followed by similar meetings at the divisional level (for states with a divisional structure) convened by the commissioners of the divisions and attended by chief medical officers of health from the districts and municipal corporations. Meetings were then held at the district level, attended by the district health officers and primary health centre medical officers. Lastly, searchers and

Table 15.16. India: number of special epidemiologists working in the field, October 1973–July 1975

State	October 1973		January 1974		June 1974		January 1975		July 1975	
	International	National	International	National	International	National	International	National	International	National
Uttar Pradesh	5	5	6	6	9	18	11	13	6	8
Bihar	2	3	4	6	17	18	28	20	10	19
West Bengal	2	0	2	0	3	0	2	0	7	2
Madhya Pradesh	2	3	3	4	1	5	2	2	0	2
Eastern states	0	2	0	1	0	4	0	5	1	8
Other states	2	0	3	0	3	1	3	0	3	0
Subtotal	13	13	18	17	33	46	46	40	27	39
Total	26		35		79		86		66	

Plate 15.9. Project vehicles in Patna, Bihar State, at the beginning of the programme.

supervisors at each primary health centre were instructed in the specific techniques of search, outbreak containment and reporting. Such meetings at different administrative levels were subsequently conducted before each new search; the experiences of the previous search were evaluated and additional or revised procedures implemented.

To organize the numerous meetings and to develop strategy over the extensive area involved required an extraordinarily intensive effort on the part of the Central Appraisal Team. As an illustration of this endeavour, one may cite the experience of a member of the team who travelled more than 1800 kilometres by car in 5 days, during which he participated in 7 district and regional meetings. To do so necessitated driving all day and through the night; the team member and his driver shared this task, alternately driving and sleeping in the cramped Jeep.

The organizational plan called for one search worker to visit one village or section of a city each day. The hundred or more villages in each primary health centre area were divided up among the staff of 15–20 health workers. To facilitate supervision, a search schedule determined which worker would be in which village on which date. Each search was planned to be completed within 7–10 days. A supervisor oversaw the work of 4 or 5 workers and was assigned villages to be checked at random.

The searchers were instructed to show the WHO smallpox recognition card (see Chapter 10, Plate 10.11) and to inquire about any suspected cases that had occurred during the preceding 2 months. All village leaders and watchmen were to be contacted, as well as schoolteachers and their pupils, and persons congregating in tea-shops and market areas. Two or 3 houses in each of 4 parts of a village and the section of a village or town in which the poorest families lived were also to be visited. When the teams travelled from village to village, they were instructed to stop at brick kilns, bus stands, migrant camps and festivals to solicit reports of possible cases of smallpox.

Suspected cases were to be notified immediately to the primary health centre physicians, who were asked to verify the diag-

nosis. In addition to the assessment of work by the supervisors, each primary health centre medical officer was expected independently to assess one village or urban area assigned to each supervisor; each district-level supervisor was expected to visit one village, one school and one market in each primary health centre area; and each state surveillance team was expected to check 100 villages, 10 markets and 30 schools after each search. Areas selected for assessment were the least accessible villages and those most distant from the primary health centre. It was assumed that if the work was well done in the more distant and difficult areas, it was likely to be satisfactory in the areas easy of access. Radio, press, and other media were utilized to inform the public where to report cases of smallpox.

The first searches in the highly endemic states began in September. With such large populations and with so many health staff involved, the logistic requirements were formidable, as will be appreciated from the following inventory of material supplied to West Bengal for its first search: 100 copies of the Operational Guide; 10 000 small smallpox recognition cards and 3000 large recognition cards; 100 copies of each district map to be used to plan search workers' schedules; 3000 copies of the searchers' village-by-village schedules; 16 000 copies of forms for recording the results of the village visit; 400 copies of forms for listing outbreaks; and 3000 copies of the weekly reporting form to be dispatched from the primary health centres to the district. For a country-wide search, it was calculated that 8 tonnes of forms would be necessary.

Because of floods, only 9 out of 16 districts in West Bengal could be reached during the September search; but only 75 cases of smallpox were detected. It was uncertain whether the search had been good and the few cases that existed had been found, or whether it had been poor and many cases had been missed. However, a more extensive search conducted throughout the state in early October identified only 143 infected villages among West Bengal's 38 000 villages and 137 towns. Moreover, Calcutta, which many had feared might harbour extensive foci, had far fewer cases than had been expected.

The encouraging reports from West Bengal were quickly followed by alarming—almost unbelievable—reports from Uttar Pradesh and Bihar. During the week preceding the search, only 354 cases in 21 districts had been reported in Uttar Pradesh and only 134 cases in 8 districts in Bihar. However, the 1-week October search revealed 1525 outbreaks with 5989 cases in Uttar Pradesh and 614 outbreaks with 3826 cases in Bihar (Fig. 15.15; Table 15.17). It should be noted, however, that outbreaks occurred in only

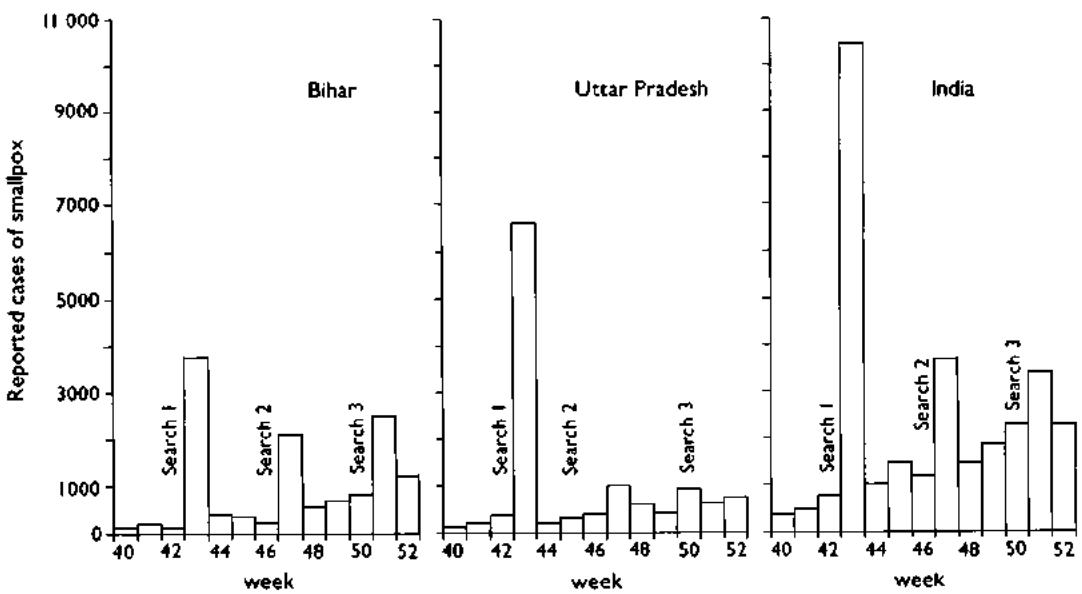


Fig. 15.15. Bihar State, Uttar Pradesh State, and India as a whole: number of reported cases of smallpox, by week, showing results of special searches, October–December 1973.

Table 15.17. Bihar, Uttar Pradesh and Madhya Pradesh: results of the 1973 search for outbreaks of smallpox

State	Month of search	Number of towns and villages	Number of villages with new outbreaks (% of total)	Number of municipalities with new outbreaks	Total number of new outbreaks found	Number of new cases found
Bihar	Oct.	67 727	601 (0.9)	13	614	3 826
	Nov.		484 (0.7)	21	505	2 459
	Dec.		385 (0.6)	20	405	2 619
Uttar Pradesh	Oct.	112 854	1 483 (1.3)	42	1 525	5 989
	Nov.		390 (0.3)	24	414	1 711
	Dec.		309 (0.3)	22	331	1 148
Madhya Pradesh	Nov.	71 116	164 (0.2)	6	170	1 216
	Dec.		51 (0.1)	2	53	215

1.3% of all villages in Uttar Pradesh and in only 0.9% in Bihar. However, smallpox was found in 42 out of the 293 municipalities in Uttar Pradesh, in 13 out of 161 in Bihar, and in almost all districts of both states.

The staff had cause for alarm because, in October, smallpox incidence was at a seasonal low. Moreover, the percentage of villages then infected was equivalent to the percentage infected *at any time* during the course of an entire year in the studies by Dr D. B. Thomas and his colleagues in Sheikhupura District in Pakistan (Thomas et al., 1972; see Chapter 14). Until this time, Sheikhupura District had been considered to be the prototype of a district with an unusually high incidence of smallpox in the generally well-vaccinated Indian subcontinent.

Despite the extensive planning and training, assessment revealed that many villages, indeed entire areas, had not been searched, and thus even the high figures recorded understated the problem. With smallpox present throughout both states and in many urban areas, it was apparent that when transmission rates increased, a major epidemic would be possible. In neither state were the health services functioning well and a 3-month period of intensive training and supervision provided little time in which to improve the performance.

The November and December searches were more thorough than the October search. Nevertheless, the number of infected villages which were discovered decreased in both states—more sharply in Uttar Pradesh, suggesting that the new strategy was having an impact. In Madhya Pradesh, geographically India's largest state, the first search was delayed until November because of floods. The results there were highly encouraging. Only 170 outbreaks were found in November and only 53 in December.

Searches in 8 "low-incidence" states revealed only 4 with outbreaks and, during 2 separate searches, fewer than 200 cases were discovered in each (Table 15.18).

Of 10 states which had been expected to be free of smallpox by September, only Andhra Pradesh was found to have had outbreaks, and, in all, only 197 cases were discovered (Table 15.19).

As 1973 ended, it was apparent that large areas of India had remained free of smallpox (Fig. 15.16), and the search programme had confirmed this. In December only 6 states recorded 100 or more cases, and 2 of them—Bihar and Uttar Pradesh—accounted for 84% of the total (Table 15.20; Fig. 15.17). Although the total number of cases recorded in India was 88 114, the highest since 1958, reporting was far more complete than it had ever been.

The autumn campaign had shown that it was possible to mobilize health resources effectively throughout entire states to search for cases and to contain outbreaks. However, with smallpox still widely prevalent in the 4 central states and the period of high transmission again beginning, it was clear that Phase Two of the campaign had to be extended into 1974.

In early January 1974, Henderson had meetings in New Delhi with Indian and WHO staff to assess possible strategies and needs for the coming months. The situation was critical. If the intensified search campaign was to continue, a commitment of additional funds was urgent. Funds earmarked for India in the WHO regular budget were sufficient to cover the campaign activities for 2–3 more months at most. To obtain additional money from WHO was a problem. WHO's budget for smallpox eradication had remained at a constant level since 1967. The funds had been proportionately

Table 15.18. India: searches for outbreaks of smallpox in low-incidence states and union territories, 1973

Low-incidence state or union territory	Number of searches	Average number of villages searched	Personnel complement	Number of outbreaks revealed	Number of cases revealed
Chandigarh	2	25	39	0	0
Gujarat	1	11 145	4 000	0	0
Haryana	2	7 840	1 500	1	1
Jammu and Kashmir	2	3 233	650	53	183
Maharashtra	2	17 954	2 563	0	0
Orissa	2	57 519	4 384	22	135
Punjab	1	12 564	1 500	0	0
Rajasthan	2	29 432	1 029	24	130
Total	–	139 712	15 665	100	449

Table 15.19. India: searches for outbreaks of smallpox in smallpox-free states or union territories, 1973

Smallpox-free state or union territory	Number of searches	Average number of villages searched	Personnel complement	Number of outbreaks revealed	Number of cases revealed
Andhra Pradesh	2	19 079	4 592	23	197
Arunachal Pradesh	1	384	138	0	0
Himachal Pradesh	3	23 998	700	0	0
Karnataka (Mysore)	1	15 565	2 636	0	0
Kerala	2	272	633	0	0
Manipur	1	1 068	138	0	0
Meghalaya	2	3 470	200	0	0
Mizoram	1	380	87	0	0
Tamil Nadu	1	16 799	2 654	0	0
Tripura	1	1 874	200	0	0
Total	–	82 889	11 978	23	197

Table 15.20. India: number of reported cases of smallpox, by state and union territory and by month, 1973

State or union territory	Population[a] (millions)	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
South[b]														
Andhra Pradesh	46.9	202	194	197	91	179	74	70	13	50	81	83	61	1 295
Goa, Daman and Diu	0.9	0	0	0	0	0	0	0	0	0	0	0	0	0
Karnataka (Mysore)	31.6	0	0	5	0	0	0	1	0	0	0	0	0	6
Kerala	23.0	0	0	0	0	0	0	0	0	0	0	0	0	0
Maharashtra	54.3	1	27	23	8	16	45	34	3	0	0	1	0	158
Orissa	23.7	27	121	365	275	137	173	52	51	23	36	78	38	1 276
Tamil Nadu	44.4	0	1	1	1	0	0	0	0	0	0	0	0	3
East														
Arunachal Pradesh	0.5	0	0	0	0	0	0	0	0	0	0	1	1	2
Assam	15.8	0	28	13	33	26	51	18	19	35	21	80	134	458
Manipur	1.2	0	0	11	2	0	0	0	0	0	0	0	0	13
Meghalaya	1.1	0	0	0	0	0	0	0	0	4	0	0	26	30
Mizoram	0.4	0	0	0	1	0	0	0	0	0	0	0	0	1
Nagaland	0.6	0	0	0	0	0	0	0	0	0	45	0	0	45
Tripura	1.7	0	0	0	1	2	6	0	0	0	0	0	0	9
West														
Chandigarh	0.3	0	0	0	0	0	0	0	0	0	0	0	1	1
Delhi	4.4	17	17	21	43	36	18	5	2	2	6	0	1	168
Gujarat	28.8	7	0	0	0	0	1	1	0	0	0	0	0	9
Haryana	10.8	40	22	10	18	23	61	7	6	0	0	1	0	188
Himachal Pradesh	3.7	0	0	1	1	0	0	0	0	0	0	0	0	2
Jammu and Kashmir	5.0	20	12	4	111	120	75	65	56	31	39	117	291	941
Punjab	14.6	6	31	9	3	6	7	0	3	0	0	0	0	65
Rajasthan	27.8	123	217	151	168	67	78	31	0	0	0	24	18	877
Central														
Bihar	60.7	632	1 226	1 274	2 639	1 773	934	1 382	596	548	4 582	3 330	5 321	24 237
Madhya Pradesh	44.9	376	535	460	364	685	372	267	321	81	215	1 219	505	5 400
Uttar Pradesh	95.2	2 784	2 044	3 650	3 689	4 990	2 159	1 226	961	437	7 481	2 348	2 675	34 444
West Bengal	47.8	2 130	2 763	3 027	3 316	2 358	1 517	949	795	314	402	418	497	18 486
Total		6 365	7 238	9 122	10 764	10 418	5 571	4 108	2 826	1 525	12 908	7 700	9 569	88 114

[a] Population estimates based on United Nations (1985) data for all India proportionately allocated by state on the basis of the 1971 census.
[b] No cases were reported during this period in the union territories of Andaman and Nicobar Islands, Dadra and Nagar Haveli, Lakshadweep, and Pondicherry.

allocated to each of WHO's regional offices in 1967 and the proportions had not changed thereafter. With the certification of eradication in the Americas in 1972, it had been requested that the 1973 allocation for that region should be transferred to the South-East Asia Region. However, the proposal was turned down. Within the South-East Asia Region, some diversion of funds from Indonesia, now free of smallpox, was possible but the amount was not great. Meanwhile, repeated appeals to governments for support had brought generous donations of vaccine but little cash. A further emergency appeal was considered but thought to be futile because governments could seldom respond to such requests in less than several months to a year. Although the programme in India had achieved a momentum which offered hope of success, little could be done without additional resources and there appeared to be no solution forthcoming. Henderson returned to Geneva to consult the newly elected Director-General, Dr Halfdan Mahler. Later that week the WHO Executive Board was to meet. On the agenda was the question of how to use US$900 000 allocated to China, a new Member State of WHO, which had declined to accept WHO funds provisionally allotted for the support of its health programmes. The Director-General agreed immediately that a cable could be sent to India indicating that these funds would be used for its smallpox eradication programme, a decision later endorsed by the Executive Board. Another emergency in an apparently never-ending series of financial crises in the programme had been averted.

The Darkest Months of the Programme, January–June 1974

In January 1974 optimism prevailed. Funds were available to continue the programme, case notification was far more complete than ever before, and the search programmes were showing steady improvement in all states. In Bihar, in which the greatest numbers of cases were being recorded and the health services were the least adequate, the programme office reported that 50% more villages had been visited during the third search, in December 1973, than during the first in October. Despite a more extensive search and despite seasonally higher transmission rates, fewer villages with new outbreaks had been found.

The results in Uttar Pradesh had been even better, with the number of newly found outbreaks declining from 1525 in October to 331 in December. Progress in West Bengal was no less encouraging. There, Arita had introduced a new system to document progress in the programme. From October

Plate 15.10. Implementing the search programme required extensive field work by national and international staff. **A**: Ram Rakha Arora (b. 1925), an Indian member of the Central Appraisal Team in West Bengal. **B**: *Left*: Lawrence Brent Brilliant (b. 1944), an epidemiologist from the WHO Regional Office for South-East Asia; *right*: Anatolij N. Slepushkin (b. 1929), an epidemiologist from the Smallpox Eradication unit at WHO Headquarters.

1973, each newly discovered outbreak was added to a master list as an "active outbreak" and not removed from the list until 4 weeks had elapsed since the last case. At the end of December, there were only 124 active outbreaks in the whole of that populous state. In Madhya Pradesh, the last of the 4 key central states, a search conducted during 7–12 January 1974 revealed only 49 new outbreaks, two-thirds of which consisted of 3 cases or less. Of 5000 outbreaks discovered in these 4 states between October and December, it was estimated that not more than 1700 were still active. In the other states, the number of reported cases—many of them resulting from importations—remained low. Meanwhile, Bangladesh reported that only 172 of its villages were infected; in Nepal, virtually all outbreaks were said to have resulted from importations.

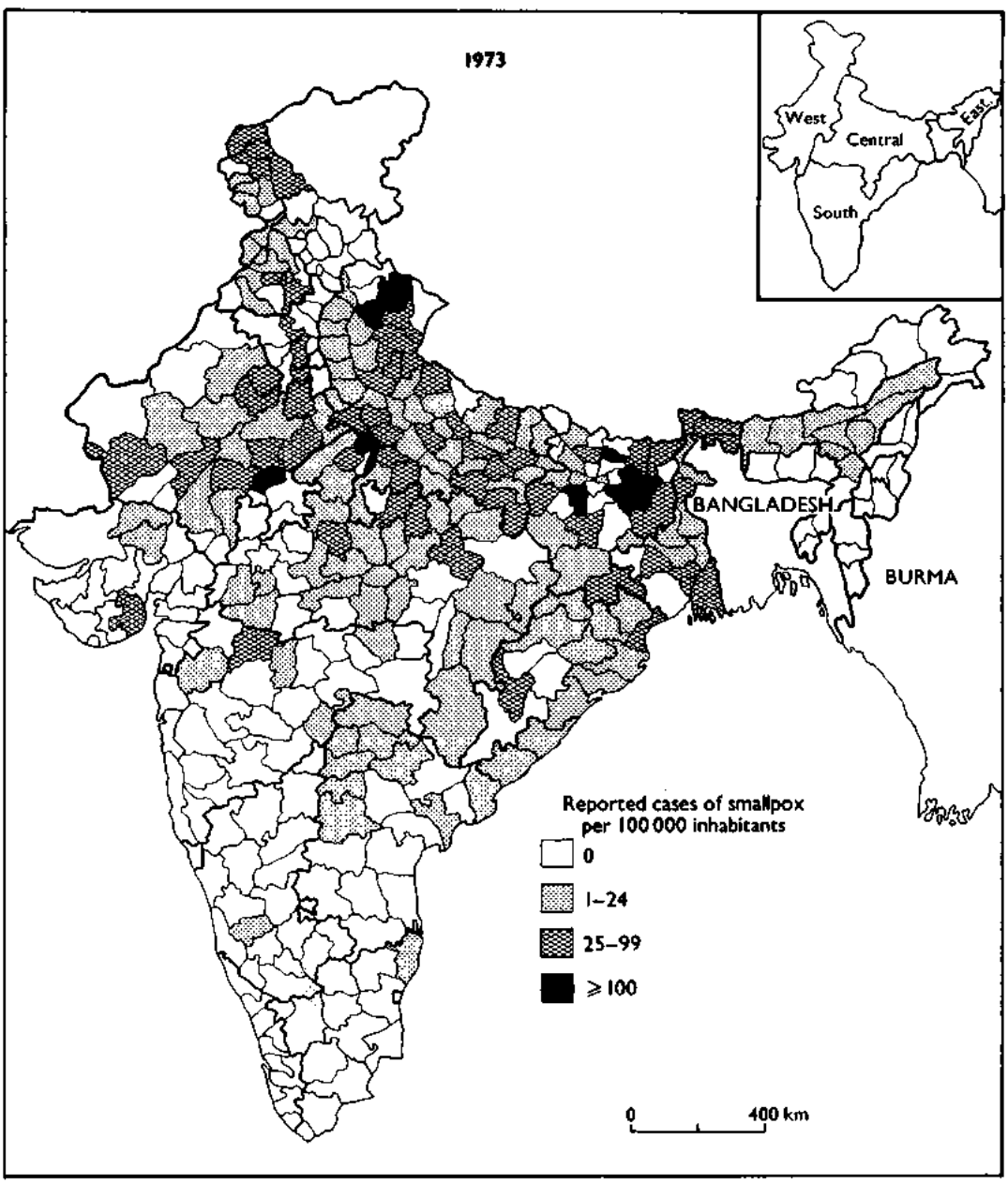


Fig. 15.16. India: number of reported cases of smallpox per 100 000 inhabitants, by district, 1973.

The Dedication of the Smallpox Programme Staff

The commitment and determination of staff who worked in the programme were extraordinary and indeed might well be the subject of a separate book. The meeting in New Delhi on 1 January 1974 of the Indian and WHO Central Appraisal Team and Henderson provides an illustration. All members of the team had been working a 7-day-week for nearly 4 months, travelling to some of the country's most remote and inhospitable areas in a frantic effort to motivate the army of health workers to contain the vastly larger number of outbreaks than anyone had foreseen. All had lost weight and were exhausted, one person had incapacitating renal colic, a second a painful facial herpes zoster infection, a third a serious fungus infection of the foot (which eventually required surgery) and a fourth atypical pneumonia with high fever and pleuritic pain. The only question asked at the meeting was how to find additional resources to sustain the momentum. When Henderson expressed scepticism of their own ability to work, let alone to continue the schedule proposed even if given the needed resources, the reply was simply: "We've considered the question and have decided that things can't get worse; therefore they must get better".

Exemplifying this determination in the field was a 50-year-old Indian professor of social and preventive medicine, Dr T. P. Jain, who was assigned as an epidemiologist in a flood-stricken area of Assam. Investigation and containment of many of the outbreaks required wading from house to house in areas in which leeches were legion and snakes a problem. A devout member of the Jain religion, he had requested a week's leave to attend ceremonies in another state commemorating the 2500th birthday of Mahavira, founder of the religion, a long-anticipated and sacred event. Another epidemiologist, arriving in the area to check the existing outbreaks in Jain's absence, found him waist-deep in water trudging from house to house, unwilling to leave for even a day so long as smallpox persisted in his area.

The commitment of the government to the programme was demonstrated early in 1974, when Dr Sharma was promoted to the position of Commissioner of Rural Health while retaining responsibility for smallpox eradication. Dr Sharma was widely known and respected among professional health staff and politicians alike for his expertise in the field of communicable diseases and for his executive ability. He had the full support of the Minister of Health and Family Planning, Dr Karan Singh. His commitment to the surveillance–containment strategy was total, and this he communicated to national and state officials on frequent visits to the field. It was important that he did so because the Director-General of Health Services, to whom he was subordinate, adhered to the traditional view that only a thorough mass vaccination campaign could succeed in eradicating smallpox, a view he expressed on frequent occasions. In part because of this contradictory advice, state officials in Bihar and occasionally in Uttar Pradesh were to call periodically for the suspension of search and containment activities in favour of total mobilization for a mass campaign to vaccinate everyone in the state. The mass vaccination approach was more easily understood and although it had been demonstrably unsuccessful in the past, there was the belief that if the health personnel were *really* properly organized and motivated the objective of 100% vaccination could be achieved. Dr Sharma's appointment ensured that the basic surveillance–containment strategy would be sustained.

A summary statement appearing in a WHO South-East Asia Regional Smallpox Surveillance Report (4 February 1974, unpublished) is indicative of the optimism prevailing at the beginning of 1974:

> "The tremendous increase in smallpox activities in the region since October 1973 has had its impact. Smallpox is diminishing in many areas at a time when it traditionally increases ... proving that smallpox transmission can be interrupted even at the height of the smallpox season. Within a few weeks a decrease in the transmission of smallpox can be expected ... If programme activities can be maintained or increased, most areas in India and Bangladesh could interrupt transmission before the monsoons."

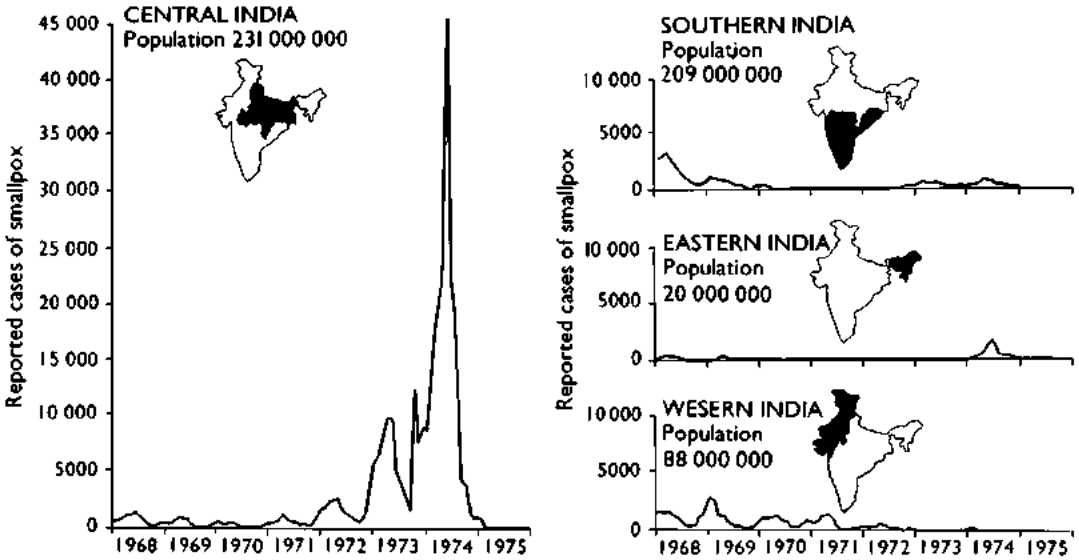


Fig. 15.17. India: number of reported cases of smallpox, by region, 1968–1975. (Population data for 1971 from Basu et al., 1979.)

BY COURTESY OF R S AGARWALA, 1974

Plate 15.11. Mudi Inder Dev Sharma (b. 1919), the Commissioner of Rural Health for India, vigorously and enthusiastically supported the programme from early in 1974 through extensive travel and personal inspiration. He is using the WHO smallpox recognition card to ask villagers in Uttar Pradesh State about possible cases of smallpox.

It was to be the last optimistic statement for many months.

In February 1974, the fourth search was conducted in Bihar. It revealed 1170 new outbreaks in villages and 18 in urban areas, almost 3 times the number (405) found in December, and more than twice as many cases as in January—10 697 as against 4816 (Table 15.21). The most seriously affected areas were the eastern districts. From here, smallpox began to spread to West Bengal (65 importations by mid-February) and to Nepal (11 importations).

Additional Indian and WHO epidemiologists were hurriedly recruited and assigned to Bihar. The fifth search (11–16 March) revealed 2374 new outbreaks, double the number found in February: more than 7000 cases were recorded during the search period (Fig. 15.18). By the end of the fifth search, there were 3682 active outbreaks in the state. Containment policies at this time called for the vaccination of residents only in the 20–30 houses adjacent to infected households. Even so, there were too few surveillance and containment teams to be able to visit more than a small proportion of the outbreaks, which were detected in many areas, and even the minimal containment measures were poorly executed. Desperate for additional help to supervise the search and containment programme, senior programme staff decided to recruit recent medical school graduates and, after a special training programme in New Delhi, 40 "junior doctors" were assigned to field work in Bihar. Eventually 140 were to participate (Jha & Achari, 1975).

Epidemic smallpox in Bihar was a problem of formidable proportions, and the occurrence of one natural or man-made calamity

Table 15.21. India: number of reported cases of smallpox, by state and union territory and by month, 1974

State or union territory	Population[a] (millions)	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
South[b]														
Andhra Pradesh	48.0	65	61	62	28	36	15	12	2	0	0	0	0	281
Karnataka	32.3	1	5	0	4	1	0	0	0	0	0	0	0	11
Kerala	23.5	0	0	2	1	1	0	0	0	0	0	0	0	4
Maharashtra	55.6	160	71	36	41	91	31	12	6	0	0	0	0	448
Orissa	24.2	53	64	347	365	564	259	211	136	43	14	10	103	2 170
Tamil Nadu	45.4	0	0	0	9	3	1	2	0	0	0	0	0	15
East														
Arunachal Pradesh	0.5	0	0	1	0	1	0	0	0	0	0	0	0	2
Assam	16.1	25	187	244	898	1 128	1 914	467	423	377	272	265	43	6 243
Manipur	1.2	0	0	0	0	4	1	0	0	5	1	0	0	11
Meghalaya	1.1	102	24	8	0	233	53	46	6	11	9	5	1	498
Mizoram	0.4	0	0	0	0	0	0	0	0	0	0	0	0	0
Nagaland	0.6	0	0	0	2	3	22	18	0	0	0	0	0	45
Tripura	1.7	0	0	0	0	0	0	0	0	0	0	0	0	0
West														
Chandigarh	0.3	0	0	0	0	0	0	0	0	0	0	0	0	0
Delhi	4.5	15	54	16	12	19	6	16	2	2	0	0	0	142
Gujarat	29.5	0	0	3	1	1	0	0	0	0	0	0	0	5
Haryana	11.1	2	4	3	23	10	18	6	5	0	0	0	0	71
Himachal Pradesh	3.8	0	0	3	1	3	0	0	0	0	0	0	0	7
Jammu and Kashmir	5.1	306	78	118	98	90	36	27	0	6	1	0	0	760
Punjab	14.9	0	2	10	5	10	18	7	0	1	0	0	0	53
Rajasthan	28.4	14	8	2	1	1	0	8	1	26	0	0	0	61
Central														
Bihar	62.2	4 816	10 697	12 788	14 553	35 626	14 971	14 076	11 591	3 416	2 758	1 053	527	126 872
Madhya Pradesh	46.0	386	310	305	358	475	157	200	44	5	0	1	10	2 251
Uttar Pradesh	97.5	2 800	2 477	3 787	4 856	8 337	6 291	4 886	1 778	698	690	195	164	36 959
West Bengal	48.9	608	721	1 819	2 428	2 196	1 795	991	342	84	61	4	45	11 094
Total		9 353	14 764	19 554	23 684	48 833	25 588	20 985	14 336	4 674	3 806	1 533	893	188 003

[a] Population estimates by states are based on United Nations (1985) data for all of India proportionately allocated by state on the basis of the 1971 census.

[b] No cases were reported during this period in the union territories of Andaman and Nicobar Islands, Dadra and Nagar Haveli, Goa, Daman and Diu, Lakshadweep, and Pondicherry.

after another further hampered the eradication effort. Indian Airlines workers went on an extended strike, making it difficult to ship vaccine and for senior personnel to travel. The railways began to be extensively used until railway workers likewise went on strike. Meanwhile, the international oil crisis had developed and, in April, petrol costs in India doubled and shortages occurred. Drought in southern Bihar, sufficiently severe to require international assistance, resulted in the migration of large populations of refugees seeking food and spreading smallpox. This was soon followed by the most severe floods in a decade in northern Bihar and even more refugees fleeing in search of food and refuge. Civil disorder and political disturbances began to occur throughout Bihar and, over large areas, government authorities were totally occupied with maintaining law and order. Throughout this period, heroic efforts were made to ensure an adequate flow of supplies and to stockpile materials such as vaccine and reporting forms in anticipation of expected shortages; however, most supplies were barely adequate to meet the current needs.

That the programme in Bihar functioned at all was remarkable and for this due credit must go to its Smallpox Programme Director, Dr A. G. Achari, a conscientious and tireless worker who, with the officers of the Central Appraisal Team, Dr Foege and Dr Dutta, sought valiantly to mobilize a lethargic health staff and to sustain morale among the Indian and WHO epidemiologists, who were overwhelmed by the explosive spread of smallpox.

When it seemed that little else could possibly go wrong, the health workers in Bihar threatened to go on strike. Dr Achari, Dr Dutta and Dr Foege sought desperately to develop a contingency plan but with little support. The observation of one district health officer was characteristic of the attitude of some supervisory health staff: "If we

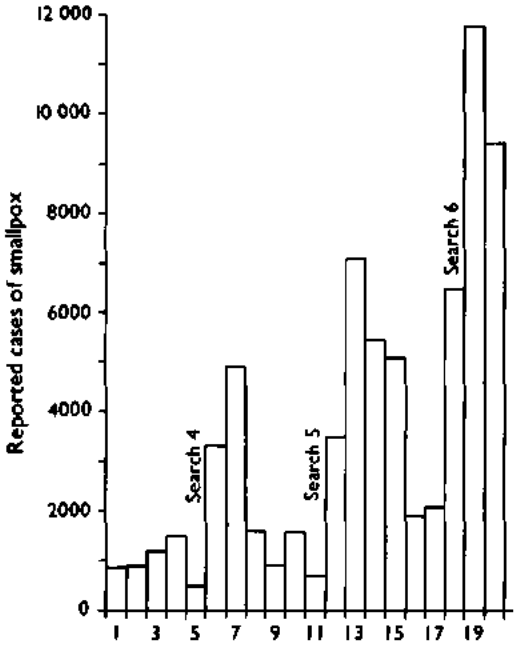


Fig. 15.18. Bihar State: number of reported cases of smallpox, by week, showing results of special searches, January–May 1974.

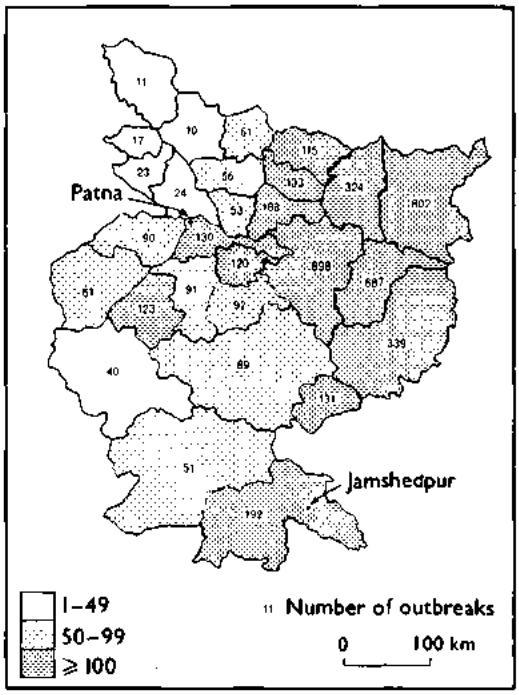


Fig. 15.19. Bihar State: number of active outbreaks of smallpox, by district, as of 5 May 1974.

don't have a strike, we don't need a contingency plan; if we do have a strike, it is no longer my responsibility."

The sixth search in Bihar (29 April–4 May) recorded 2658 additional outbreaks—the number of active outbreaks increasing to 4921. More than 7% of all villages and municipal areas in the state were infected, the most heavily afflicted being in the north-east (Fig. 15.19), where, in 3 districts, 25% of all villages were infected.

India's Director-General of Health Services, still an advocate of mass vaccination, became increasingly alarmed and advised Bihar's Minister of Health to withdraw staff from the infected areas and to begin mass vaccination campaigns in the areas still free of smallpox to prevent them from becoming infected. Dr Sharma, learning of this only after the minister in Bihar had begun to take action, protested direct to India's Minister of Health and Family Planning, Dr Karan Singh, and together they flew to Bihar to intercede. The Bihar minister rescinded his order. In an epidemic as extensive as that occurring in Bihar, some of the Indian and WHO programme epidemiologists began to speculate that Bihar might represent a special case in which the now well-tested surveillance and containment strategy might not be applicable.

Throughout May and into early June, the epidemic continued to intensify. With daytime temperatures normally exceeding 40 °C, field work became ever more difficult, morale began to deteriorate and, again, the question of a return to state-wide mass vaccination arose. The minister was more resolved than before and, in the June meeting of state and district programme officers, strongly advocated this approach. Senior programme staff argued in vain, until an Indian physician, working in one of the districts, pointed out in a deferential manner that he had grown up in a village and there, when a house was on fire, they put water on that house and not on all houses in the village. The minister reluctantly agreed to defer a mass vaccination campaign for one more month but only on the understanding that if no apparent progress had been made by then, mass vaccination would be initiated. Senior staff hoped that, even if containment were less than optimum, the seasonal decrease in transmission would partially stem the epidemic and so preserve what they believed to be the only possible effective strategy—surveillance and containment.

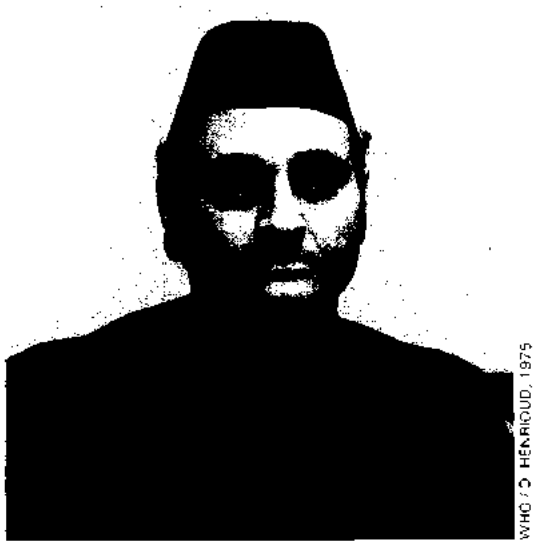


Plate 15.12. Karan Singh, Minister of Health and Family Planning of India from 1973 to 1977, provided strong political support for the programme and for the surveillance–containment strategy.

In the other states of India, the situation was better than in Bihar but not so good as had been expected in February. Uttar Pradesh was the next most heavily infected state. The numbers of reported cases and outbreaks had risen steadily since January, although less precipitously than in Bihar. A peak of 1905 active outbreaks was reached in May, with 8337 cases reported that month. Outbreaks were reported from 442 (51%) of the state's 875 primary health centres and in 47 of its 55 districts (Srivastava & Agarwala, 1975). However, 82% of the outbreaks occurred in only 15 districts, primarily in eastern Uttar Pradesh, where their large number precluded the taking of effective containment measures. Elsewhere in the state, with the support of the Director of Medical and Health Services and Family Planning, Dr G. P. Srivastava, the health staff had begun to function well.

In West Bengal, the number of active outbreaks increased steadily, from 124 in December to 556 following the seventh search in mid-April. However, more than 75% of the outbreaks took place in only 5 of the state's 16 districts, and here village volunteers began to be recruited and trained for containment operations, an effective practice later adopted in other states. The increase in the number of outbreaks in West Bengal was largely accounted for by importations, mostly from Bihar. Between January and May, programme staff documented 386 imported outbreaks, and others occurred as a result of spread from these importations.

Importations, principally from Bihar, Uttar Pradesh and West Bengal, accounted for an increase in the number of cases in Madhya Pradesh, Maharashtra and Orissa. Each state worked diligently and effectively to discover and contain the outbreaks as rapidly as possible, but by May, both the smallpox eradication staff and the general health service personnel were reaching a critical point of fatigue and frustration. Meanwhile, the eastern states, hitherto all but free of smallpox, experienced a sharp increase in the number of cases, resulting from importations from Bangladesh, Bihar and Uttar Pradesh. This was cause for additional alarm because, in the eastern states, health services were generally less extensive and not much better organized than those in Bihar. Although they were not populous states, road and rail services were poor and both search and containment activities were difficult to organize and to execute.

The unexpected and explosive epidemic of smallpox in Bihar and its spread to other states had required the mobilization of far more Indian and WHO epidemiologists (see Table 15.16) than had been foreseen and had necessitated the emergency purchase of more vehicles and supplies of all types than had been planned. By April, funds to support the smallpox programme were again at a low level. Requests were made to numerous governments for additional finances; few showed any interest and no country indicated it was in a position to act quickly in answering an appeal. Privately, many expressed scepticism about the programme's prospects of success. The reaction was not surprising in view of the fact that the number of cases of smallpox recorded in India in the spring of 1974 was the largest for nearly two decades. WHO's frequent appeals in the past for funds to bolster its malaria eradication campaign, and the continuing setbacks in that programme despite infusions of ever larger sums of money, were well remembered. Once again, the programme approached a critical point, but, unexpectedly, substantial help materialized from a new source, the Swedish International Development Authority (SIDA). In a casual conversation with the Personnel Officer of the WHO Regional Office for South East Asia—an official of Swedish nationality—Dr Grasset learned

Plate 15.13. Jarl E. Tranaeus (b. 1923), Head of the Development Co-operation Office of the Swedish Embassy in New Delhi from 1973 to 1978, persuaded Swedish authorities and the Indian government's Planning Commission of the need for substantial additional assistance to the smallpox eradication programme at a crucial moment.

that SIDA planned to examine alternative uses for Swedish funds which had become available because of the cancellation of another project in India. Discussions promptly followed with Mr J. Tranaeus, at the Swedish Embassy in New Delhi. Convinced, as few others were, that an effective and well-directed campaign was in progress whatever the smallpox incidence might suggest, he persuaded the Planning Commission of the government of India, as well as his superiors in Stockholm, of the merits of the programme. Within a few weeks, a memorandum of agreement had been signed on behalf of the governments of India and Sweden which made available to WHO US$2.8 million in support of the smallpox programme. With Mr Tranaeus's continuing enthusiastic interest, SIDA was eventually to provide US$10 million to the programme. The government of India also increased its own central allocation of funds. For 1974, a sum of US$13 million was made available for field operations.

Time was required to effect the necessary transfer of funds, but the Division of Budget and Finance in WHO Headquarters readily agreed to permit funds to be obligated even though they were not yet in hand. Meanwhile, the administrative staff in the WHO regional office were experiencing difficulties, because of the substantial expansion in the number of personnel in the programme receiving a stipend from WHO, the larger numbers of imprest accounts to be handled and the need to procure a greater volume of supplies (Table 15.22). It was essential that additional personnel should be recruited and that budget and finance operations should be established for the programme. The Center for Disease Control (formerly the Communicable Disease Center) in Atlanta, which was already providing many field epidemiologists, responded to this need by sending its most capable senior administrative staff to help to bring some order into an increasingly chaotic administrative situation. Beginning with the Center's Deputy Director, Mr William Watson, an exceptionally imaginative group of administrators worked tirelessly with the group of no less talented WHO administrative staff to provide essential services in support of the field staff.

Although the smallpox epidemic was featured more often and with greater prominence in Indian newspapers, little was known of the problem outside the country. However, in May 1974, the epidemic became international news. On 18 May 1974, India tested its first atomic device in an underground explosion in Rajasthan. At that time, the smallpox epidemic was at its height, more than 11 000 cases being reported in a single

Table 15.22. India: principal supplies and items of equipment provided by WHO, 1970–1976[a]

Item	1970	1971	1972	1973	1974	1975	1976	Total
Vehicles	0	48	36	37	191	36	0	348
Motor cycles	47	0	45	0	175	130	0	397
Bifurcated needles (thousands)	878	907	1 000	300	976	1 600	1 035	6 696

[a] Between 1972 and 1976, it is estimated that WHO, in addition, arranged to print and distribute the following material: approximately 31 million forms for use in reporting and in search and containment operations; 500 000 booklets for use in outbreaks and in market searches; 400 000 posters; 1 million smallpox recognition cards; and 500 000 other guides and miscellaneous publications.

week. International news reporters who had flown to India to cover the atomic test arrived just as the smallpox epidemic hit the headlines in the local press; international media coverage of both events was extensive. Programme staff repeatedly explained that more complete reporting accounted in major part for what appeared to be the largest epidemic for many years, but scepticism was prevalent and understandable.

Although the problem in Bihar was serious, the eradication programme throughout India was steadily improving and gaining momentum. Week-long village-by-village searches were being performed each month throughout the high-incidence states and less frequently in the others (Table 15.23). The number of those engaged in the searches was increasing (Table 15.24).

As serious and frustrating as the situation appeared, yet another disaster aggravated it—the Jamshedpur epidemic in Bihar State. Its discovery resulted from investigations in Madhya Pradesh. Special efforts had been made to interrupt transmission in Madhya Pradesh. It was one of the 4 central states considered to be of highest priority, and was geographically the largest state in India, with a population of 46 million. Most of the outbreaks which had been discovered during the autumn searches were in the northern and eastern districts of the state, bordering on Bihar and Uttar Pradesh. The December 1973 search had revealed only 215 cases and 53 new outbreaks. By the beginning of March 1974, and after 5 monthly searches of its 10 million households, smallpox appeared to be present in only a single, geographically limited focus, in a tribal area and one of the least developed parts of the state.

Table 15.23. India: frequency of active searches for outbreaks of smallpox, 1973–1975

State or union territory[a]	Number of searches		
	1973	1974	1975
High-incidence:			
Bihar	3	11	9
Madhya Pradesh	2	10	4
Uttar Pradesh	3	10	10
West Bengal	4	12	12
Low-incidence:			
Chandigarh	2	2	5
Delhi	0	3	4
Gujarat	1	3	5
Haryana	2	4	4
Jammu and Kashmir	2	6	6
Maharashtra	1	5	6
Orissa	2	5	6
Punjab	1	3	5
Rajasthan	2	2	4
Smallpox-free:			
Andhra Pradesh	2	7	4
Arunachal Pradesh	1	6	12
Assam	0	8	11
Goa, Daman and Diu	0	0	2
Himachal Pradesh	3	2	6
Karnataka	1	5	3
Kerala	2	3	5
Manipur	1	5	11
Meghalaya	2	8	11
Mizoram	1	6	9
Nagaland	0	4	11
Pondicherry	0	0	1
Sikkim	0	0	1
Tamil Nadu	1	4	6
Tripura	1	6	11
Total	40	140	184

[a] Relative incidence as defined in 1973.

Table 15.24. India: approximate number of workers, per search, 1973–1976

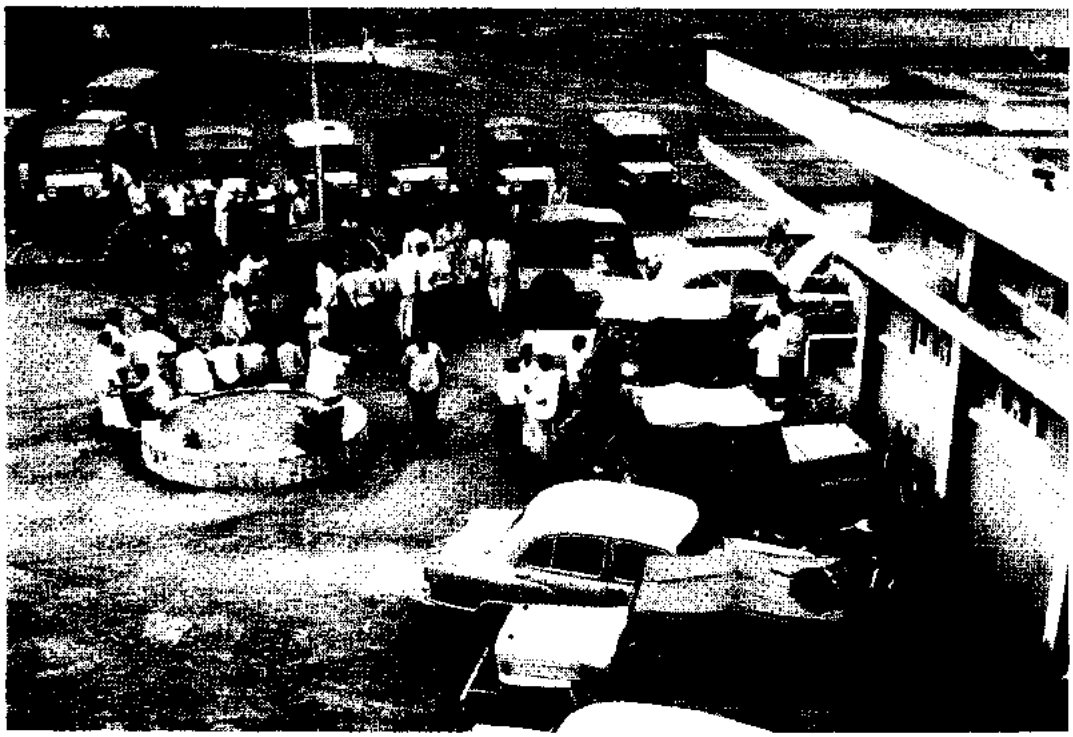
Year	India, total	High-incidence states	Low-incidence states	Smallpox-free states
1973	63 890	36 073	16 592	11 225
1974	80 847	35 509	33 916	11 422
1975	116 829	39 404	45 001	32 424
1976	134 412	43 688	54 261	36 463

In late March 1974, however, reports of smallpox outbreaks began to arrive from many areas of Madhya Pradesh which had been considered to be smallpox-free. Investigations revealed these to be the result of recent importations from the neighbouring state of Bihar. The source of infection of many was traced to an industrial complex in southern Bihar: Jamshedpur in Singhbhum District. *Adivassis* (tribal people) often travelled 300–800 kilometres to Jamshedpur from their homes in Madhya Pradesh in search of seasonal employment. If they became ill with fever, they returned to their native villages, where many subsequently developed rash and spread smallpox to others.

Dr Brilliant was dispatched to Jamshedpur in late April to assess the situation. He found a major problem of unexpected magnitude.

The epidemic in Jamshedpur, Singhbhum District, Bihar

The Jamshedpur industrial complex is one of India's most important steel-producing areas, its prosperity contrasting sharply with economically depressed neighbouring areas of southern Bihar, eastern Madhya Pradesh



BY COURTESY OF TATA INDUSTRIES

Plate 15.14. The office of Tata Industries, Jamshedpur, became the smallpox eradication headquarters for Chotanagpur Division, Bihar State.

and northern Orissa. As such, it attracted numerous seasonal workers, beggars and transients.

The special investigation began in early May. The District Medical Officer of Singhbhum disclosed that during the preceding 6 weeks, he had received 125 notifications of outbreaks in other districts of Bihar and in other states which were suspected of having originated in his district, and that 12–15 notifications were then being received daily. Little action had been taken, the government health structure in this district being poor. In addition to 27 primary health centres that reported to him, all of which were then known to have smallpox cases, there were 15 autonomous and separately administered health units in Jamshedpur (population, 800 000). The health units included small company towns, corporations, large colonies of railway employees and others. No one was charged with the task of reporting cases among the large migrant population, and the railways denied all responsibility for the reporting of cases from the areas they administered. Half the health units were found still to be using rotary lancets.

At the industrial complex, a group of heavy industries of the Tata group, officials professed ignorance of the problem but immediately agreed to provide help in a search of the city and of 1760 villages within a 45-kilometre radius. In a search that took place in mid-May, 50 physicians, 200 paramedical supervisors and 900 searchers discovered 1479 cases in the city and 726 cases in the 456 villages found to be infected (Basu et al., 1979). An intensive programme of containment and case detection was immediately undertaken. This involved, in addition to government and WHO health staff, personnel and transport provided by 7 of the Tata industries as well as voluntary organizations, including the Rotary Club, the Lions Club, the Bihar Flying Club, the local blood bank and the All-India Women's Council (Bharucha, 1975). All bridges and major roads were barricaded and no one was permitted to pass unless vaccinated. A special programme dealt with railway travellers, especially third-class passengers, of whom perhaps one-third travelled without tickets. Trains were diverted to special platforms, which permitted all passengers to be checked

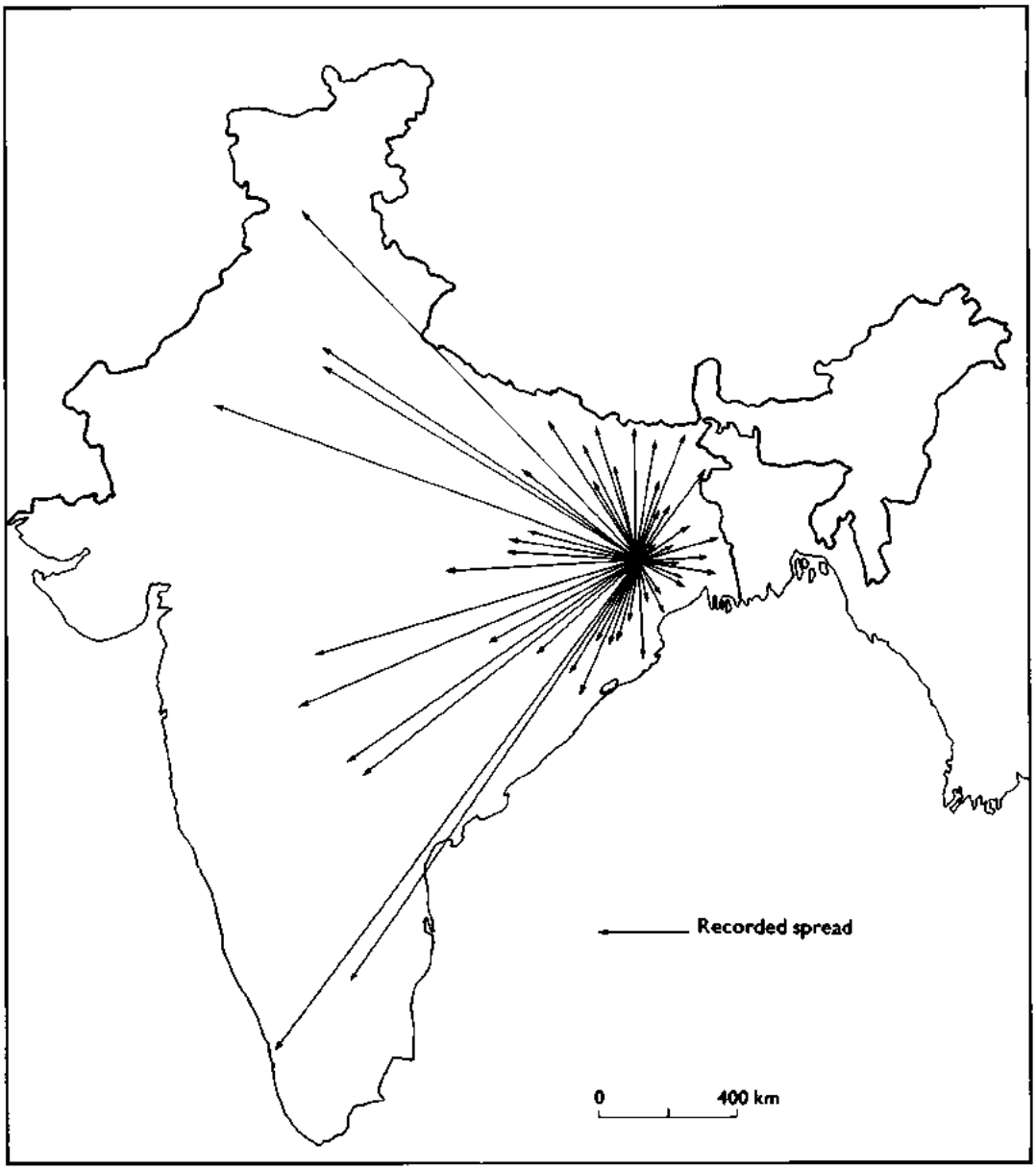


Fig. 15.20. Spread of smallpox from the Jamshedpur urban industrial complex to the rest of India, 1974.

when boarding or leaving a train. Checkpoints were established at bus stations, and employers ensured that workers and their families were vaccinated. Meanwhile, the containment of all known outbreaks began, an effort which in fact necessitated house-to-house vaccination of the entire urban complex and most of the surrounding villages.

Two months were required to bring the epidemic under control. Meanwhile, 300 outbreaks and at least 2000 cases occurred in 11 states of India and in Nepal as a result of travel from Jamshedpur (Fig. 15.20). The area most affected was Bilaspur District (Madhya Pradesh), with 484 cases in 72 villages.

A Redoubled Effort, June–December 1974

Early June 1974 was the psychological low point of the Indian smallpox eradication programme, if not of the global Intensified Programme itself. A 9-month intensive campaign had been conducted throughout India

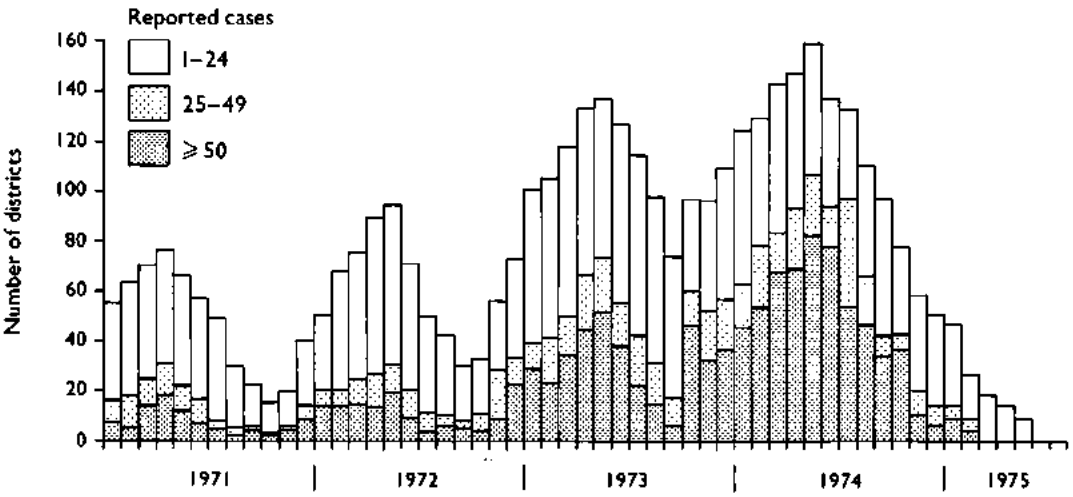


Fig. 15.21. India: number of districts reporting cases of smallpox, by month, 1971–1975.

with senior staff and numerous field staff working 7 days a week. Despite the large expenditure of money and effort to date, and despite what appeared to be an increasingly successful effort in surveillance and containment activities, there were 8664 known outbreaks. Moreover, up to the end of May, India had already recorded 116 188 cases, a number greater than that reported for the entire world during any of the preceding 6 years of the Intensified Programme. Cases were reported in May from nearly one-third of the districts in India, of which 80 reported 50 cases or more (Fig. 15.21). Many areas of India remained free of smallpox or had only a few outbreaks resulting from importations (Fig. 15.22), but the epidemic wave then surging through Bihar seemed to be moving both east and south. It was clear that the efforts made so far in Bihar had been inadequate to contain smallpox, and the states which appeared to be the next candidates for epidemic smallpox—Orissa to the south and the states to the east—had health services which were not much better in quality than those in Bihar.

During June, with the beginning of the monsoon period, smallpox transmission normally declined in India and the number of outbreaks diminished. However, with the disease so widely seeded throughout Bihar and adjacent areas, it was clear that unless a concerted effort were made to contain the outbreaks during the summer, smallpox would remain widely disseminated at the commencement of the next season and the experience of the spring of 1974 would be repeated. Activities of all types usually diminish in India during the summer months—the hottest, the most humid and the most difficult months of the year in which to work. A staff which had toiled to the point of exhaustion between September and May would have to mount one more effort.

On 17 June 1974, the Central Appraisal Team met the Secretary of Health and the Director-General of Health Services to discuss an emergency programme for the whole of India, but especially for Bihar. It was decided to increase the number of special epidemiologists from the 50 who were in the field at the time to more than 100. WHO would initially provide 12 additional international epidemiologists, and 6 non-medical surveillance officers; the government of India would attempt to recruit 40 epidemiologists. If that proved impossible, WHO would try to obtain the services of more international epidemiologists.

Six central-level surveillance teams would be established which would respond to emergency smallpox problems as they developed. State surveillance teams, hitherto restricted in travel to the state in which they were assigned, would be directed to cross state borders whenever necessary to seek the source of infection of outbreaks.

Three hundred additional containment teams would be recruited, each to be headed by recent Indian medical graduates. A further 375 Jeeps would be purchased or hired. To

fund these activities, SIDA offered additional financial assistance, which was rapidly made available.

It was recognized that special efforts would be required in Bihar. Following consultations between the staff of the WHO regional office, the Governor and the State Health Minister, the Chief Secretary of the State of Bihar sent a special letter to all district magistrates, informing them that as from the end of June they and the block development officers would assume responsibility for the conduct and organization of the campaign in their districts. Dr Achari would continue in his role as State Smallpox Eradication Programme officer but more effective senior administrative staff would replace the health service staff in bearing primary responsibility for the programme.

The president of Tata Industries was

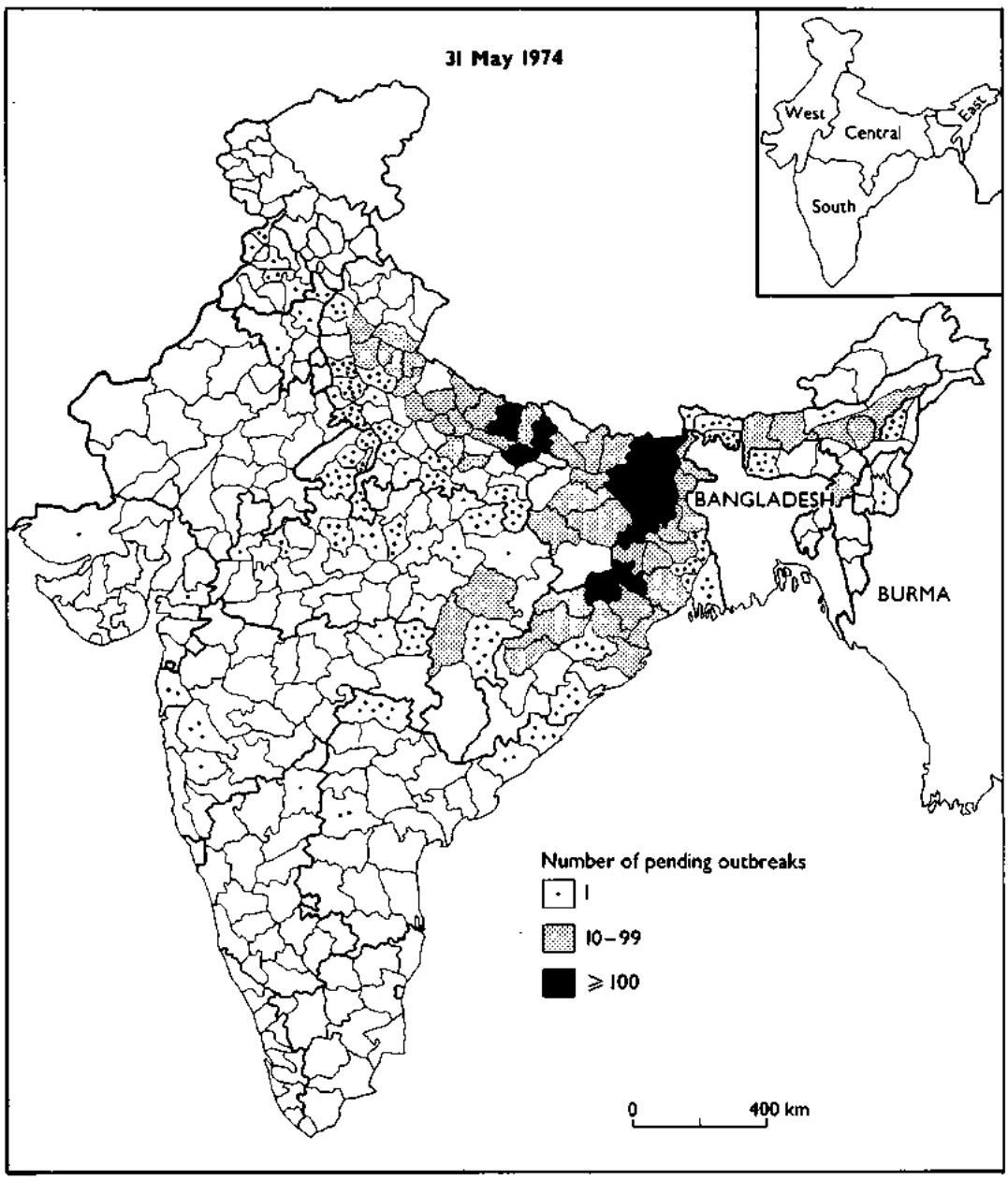


Fig. 15.22. India: number of pending outbreaks of smallpox, by district, as of 31 May 1974.

The Situation in India as Seen in June 1974

Memorandum, dated 24 June 1974, from the Chief of the WHO Smallpox Eradication unit to all smallpox eradication staff:

"The epidemics of smallpox now occurring in Bihar, eastern Uttar Pradesh and adjacent areas have been the subject of world-wide press interest during the past two weeks with many articles appearing in all major newspapers and news magazines. Providing perspective on the problem has not been easy. While there is no question but that Bihar and eastern Uttar Pradesh are heavily afflicted and represent now the "epicentre" of the global problem, the fact of a far more active programme and more complete reporting unquestionably magnifies the severity of the problem when comparing this year's and last year's data. Whatever the relative magnitude of the problem, it is clear that the most critical battle of the entire programme is now being fought on the Indo-Gangetic plain of Bihar, Uttar Pradesh and the adjacent states. Our success in these efforts over the coming months will be determining in regard to the goal of global eradication.

"The reporting of large numbers of cases as is now the case in Bihar, eastern Uttar Pradesh and adjoining areas, is of real concern but, at the same time, it may also be regarded as an encouraging sign. Unless outbreaks are found, they cannot be controlled. And one must recall the experience in Brazil when, in 1969, surveillance was first introduced into the programme. Smallpox incidence abruptly rose that year to reach the highest level in almost a decade, only to fall to '0' less than a year later. Can we do the same in these other problem areas? Unquestionably we can, provided there is full government support at all levels and that every effort continues to be made to find all cases and outbreaks and to contain them.

"While the epidemics in India have captured the headlines, equally newsworthy are the spectacular achievements in Pakistan. It is apparent that staff at all levels of the programme now realize that eradication is imminent and with this realization has come an even more energetic burst of activity."

approached for help in dealing with smallpox in the 6 southern districts of Bihar comprising Chotanagpur Division. He agreed to assist and the company's Board of Directors approved the expenditure of 7.2 million rupees (US$900 000) and the assignment of personnel and vehicles. An unusual semi-autonomous public and private sector programme was created in this division, involving personnel and equipment from WHO, Tata Industries, the government of India, the state of Bihar, and OXFAM, a private voluntary organization. The consortium participating in the Chotanagpur Division programme was to function capably and with remarkable cooperation over the following 12 months.

Deficiencies in the containment of outbreaks had proved to be a serious weakness of the programme in most states, particularly Bihar and Assam. Where smallpox outbreaks were few, state surveillance teams had usually assisted local staff in their investigation and in the vaccination of village residents. Where smallpox was widely prevalent, procedures called for the detection of all cases in the area and the vaccination of those in the 20–30 nearest households. The names of any absent household members were supposed to be recorded and the village visited on a later occasion to ensure that all were vaccinated. This directive was rarely followed, however. In many areas of the world, and indeed in many parts of India, simple containment measures had sufficed to stop transmission. In the more densely populated parts of India, however, they proved ineffective. Many persons left their homes during the day to go to the fields, to market or elsewhere; some who objected to or feared vaccination simply hid themselves and their children when the teams were in the villages; many visited relatives and friends, including those with smallpox, in other villages. The result was that even after intensive containment vaccination, numerous susceptible persons remained and smallpox transmission persisted.

It was therefore decided to systematize the containment activity in a manner that could be readily understood and widely applied and

Plate 15.15. One of the 56 surveillance teams in Chotanagpur Division, Bihar State, setting up camp in a tribal village. The programme in Chotanagpur, one of the most seriously affected areas, represented an unusual co-operative effort of groups from the public and private sectors.

that was subject to verification by a supervisor. "Containment books" were designed, printed and distributed in August 1974. One book was used for each outbreak. The name of each person in each of 500 houses surrounding an infected household in a rural area (1000 houses in an urban area) was to be listed in the book and repeat visits made to the village until all persons had been vaccinated and the fact duly registered in the book (Sharma & Grasset, 1975). In a separate section of the book, information regarding each case was recorded.

Three specific standards were also established at this time as indices of the effectiveness of, respectively, surveillance, containment, and outbreak investigation activities. The provision of standards by which a programme in any area could be measured was thought to be helpful in improving the quality of supervision. An indication of the degree of effectiveness of surveillance was the lapse of time between the onset of the first case and the detection of the outbreak. The detection of at least 75% of outbreaks within 14 days of the onset of the first case was felt to be attainable. If adequate containment were performed, all susceptible contacts would be vaccinated and none should develop smallpox once vaccinial immunity had developed say, after 7–12 days. Assuming that it would take several days to identify and vaccinate susceptible persons, it seemed reasonable to establish a second goal—namely, that no cases should develop more than 17 days after an outbreak was detected. The quality of the investigation of an outbreak was more difficult to measure, but such quantification was considered important because experience had shown that the least well performed part of an investigation was usually the identification of the source of infection. The concept that each individual with smallpox must have been in face-to-face contact with another individual with smallpox just 7–17 days before onset was a surprisingly difficult concept for many to grasp. On investigation forms, many simply listed "sporadic" as the source of infection. To identify the source, however, was vital because often other, as yet undiscovered, outbreaks were unearthed in this manner. Thus, the third goal called for the identification of the source of the outbreak in 90% of outbreaks, a level of success which had been achieved by competent epidemiologists in other areas.

The measurement of progress based on the number of the then existing infected villages and urban *mohallas* (sections of a city) had been initiated in October 1973 in West Bengal and had been introduced in some other states as well, particularly those with a low incidence of smallpox. In June 1974,

The Problem of Beggars

The containment of outbreaks among beggars proved to be an exceptionally difficult problem requiring imaginative and administratively unorthodox solutions. The isolation of beggars with smallpox in their homes was impossible because most were transients. In fact, isolation either in a house or in a hospital was refused because both the beggars and their families were dependent on begging for their livelihood. Even those actively ill with smallpox travelled from village to village shouting for alms, as was their custom. During 1973, a number of instances were documented in which infected beggars had transmitted smallpox to a dozen or more people and had been the source of many widely dispersed outbreaks.

In 1973 an epidemiologist wrote to propose that beggars with smallpox and their families should be given food and lodging until they recovered. The proposal was rejected by WHO regional office administrators and senior Indian staff, who foresaw this as a precedent to providing support to a legion of beggars. Undeterred, Dr Stephen Jones, a free-spirited American epidemiologist, used his imprest account funds to do just this and submitted a bill of 1800 rupees for the hiring of a house, the purchase of rice, a broom and various other supplies to house a family of beggars. Anticipating trouble in explaining the outlay to WHO's finance officer, Dr Grasset and Dr Foege decided to pay the relatively small bill themselves but argued more aggressively for a change in policy. Eventually, the practice was accepted. During succeeding months, hundreds of beggar families with smallpox were supported in this manner and effective containment of the outbreaks was achieved.

uniform definitions for this method of measurement were developed and it was formally adopted throughout India. Any village or *mohalla* in which a case had occurred within the preceding 4 weeks (subsequently extended to 6 weeks) was considered to be the site of a "pending outbreak". This concept recognized the potential for the spread of smallpox from the patient to susceptible contacts throughout the period concerned and the need to check the outbreak repeatedly to ensure that transmission did not continue. A list was kept in each primary health centre and each district (later, each state) showing the name of the infected village or *mohalla*, the date of onset of each case, the date of discovery, the date on which containment began, the source of infection, and the dates on which supervisory personnel had visited it. The outbreak was not removed from the list until the site was visited and searched again, not less than 4 weeks (later, 6 weeks) after the onset of the last case.

As at the end of June 1974, there were 6401 pending outbreaks in 17 states and Delhi Municipal Corporation (Table 15.25).

With additional resources and an increased complement of supervisory personnel, state-wide search and containment programmes continued throughout the summer. Most of the resources were assigned to Assam, Bihar, Uttar Pradesh and West Bengal, in which searches were conducted monthly. In Bihar alone, 35 national and international epidemiologists and more than 100 state epidemiologists and paramedical personnel assisted state, district and local health personnel (Jha & Achari, 1975); in Uttar Pradesh, there were 27 national and international epidemiologists and 19 state surveillance teams (Srivastava & Agarwala, 1975). Most other states conducted one search during this period, although some conducted two. The number of pending outbreaks began to decline sharply, and with fewer outbreaks surveillance teams were able to provide increasingly better supervision of search and containment activities. The quality of both procedures rapidly improved. In addition, the teams devoted more time to visiting markets and schools to inquire about rumours of possible cases. The number of pending outbreaks decreased to 4606 at the end of July and to 3267 at the end of August. The first hopeful note since February was sounded on 26 August in a WHO South-East Asia Smallpox Regional Surveillance Report: "The opportunities for interrupting smallpox transmission in India, Nepal and Bangladesh are better than at any time since the programme started."

By the end of September, there were only 2124 pending outbreaks, of which 1727

Table 15.25. India: pending outbreaks of smallpox at the end of each month, 1974–1975

State or union territory[a]	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	March	Apr.	May	June
South													
Andhra Pradesh	12	9	4	1	0	0	0	0	0	0	0	0	0
Karnataka	0	0	0	0	0	0	0	0	0	0	0	0	0
Kerala	0	0	0	0	0	0	0	0	0	0	0	0	0
Maharashtra	19	9	2	1	0	0	0	0	0	0	0	0	0
Orissa	105	46	11	8	4	4	8	2	0	0	0	0	0
Tamil Nadu	1	2	0	0	0	0	0	0	0	0	0	0	0
East													
Assam	173	87	50	64	65	31	19	5	5	8	7	3	1
Manipur	1	2	2	1	0	0	0	0	0	0	0	0	0
Meghalaya	16	7	2	1	3	2	2	7	13	4	4	0	0
Nagaland	11	6	5	2	0	0	0	0	0	0	0	0	0
Sikkim	0	0	0	0	0	0	0	0	0	0	0	0	0
Tripura	0	0	0	0	0	0	0	0	1	1	1	2	1
West													
Delhi	5	5	4	1	0	0	0	0	0	0	0	0	0
Gujarat	1	0	0	0	0	0	0	6	3	3	0	0	0
Haryana	4	4	2	0	0	0	0	0	0	0	0	0	0
Himachal Pradesh	0	0	0	0	0	0	0	0	0	0	0	0	0
Jammu and Kashmir	13	6	9	1	3	1	0	0	0	0	0	0	0
Punjab	6	6	2	1	0	0	0	0	0	0	0	0	0
Rajasthan	1	1	1	1	0	0	0	0	0	0	0	0	0
Central													
Bihar	3 874	3 320	2 697	1 727	759	251	205	110	62	15	4	4	0
Madhya Pradesh	83	29	17	1	1	1	0	1	0	0	0	0	0
Uttar Pradesh	1 640	866	360	284	131	50	45	50	20	3	0	0	0
West Bengal	436	201	99	30	14	3	6	13	9	6	15	12	0
Total	6 401	4 606	3 267	2 124	980	343	285	194	113	40	31	21	2

[a] No outbreaks were recorded in the union territories of Andaman and Nicobar Islands, Arunachal Pradesh, Chandigarh, Dadra and Nagar Haveli, Goa, Daman and Diu, Lakshadweep, Mizoram and Pondicherry.

(81%) were in Bihar (Table 15.25; Fig. 15.23). The north-eastern districts of Purnea and Katihar in Bihar had more than 600 pending outbreaks, but in only 8 other districts were there more than 50. Almost none were to be found in all of southern and western India. In September, 4674 cases were reported, one-tenth the number recorded in May.

The staff were optimistic but still concerned. The analysis of data from previous years indicated that some increase in transmission occurred at the beginning of October, coinciding with an increase in the numbers of persons travelling from place to place to attend festivals and marriages. Thus, there was a heightened concern about the spread of smallpox over greater distances. Moreover, active outbreaks persisted in 50 municipalities which were recognized to be important sites of dissemination to rural areas. Finally, in Assam, the number of pending outbreaks had actually increased from a low of 50 in August to 64 in September; in this state, field operations were greatly hampered by floods, a poor transportation network and a less than adequate health service. Its neighbour, Bangladesh, appeared to pose no threat, since there were only 163 infected villages in the country at the end of September, a competent programme was in place and the numbers of reported cases and outbreaks were declining as rapidly as in India. In Nepal, to the north, only 4 outbreaks were detected in September 1974.

Additional measures were implemented in October to strengthen surveillance and containment. In all urban areas with active outbreaks, a house-to-house search was conducted every 2 weeks. Additional personnel were assigned to work in Assam. Perhaps of greatest importance was the decision to offer throughout India a reward for the notification of a previously unreported outbreak of smallpox in which a case had occurred within the preceding 6 weeks. This, it was hoped, would permit earlier detection of cases and discourage the suppression of reports which, despite all efforts, remained a problem in some areas. In addition, smallpox cases were sometimes hidden by villagers who held

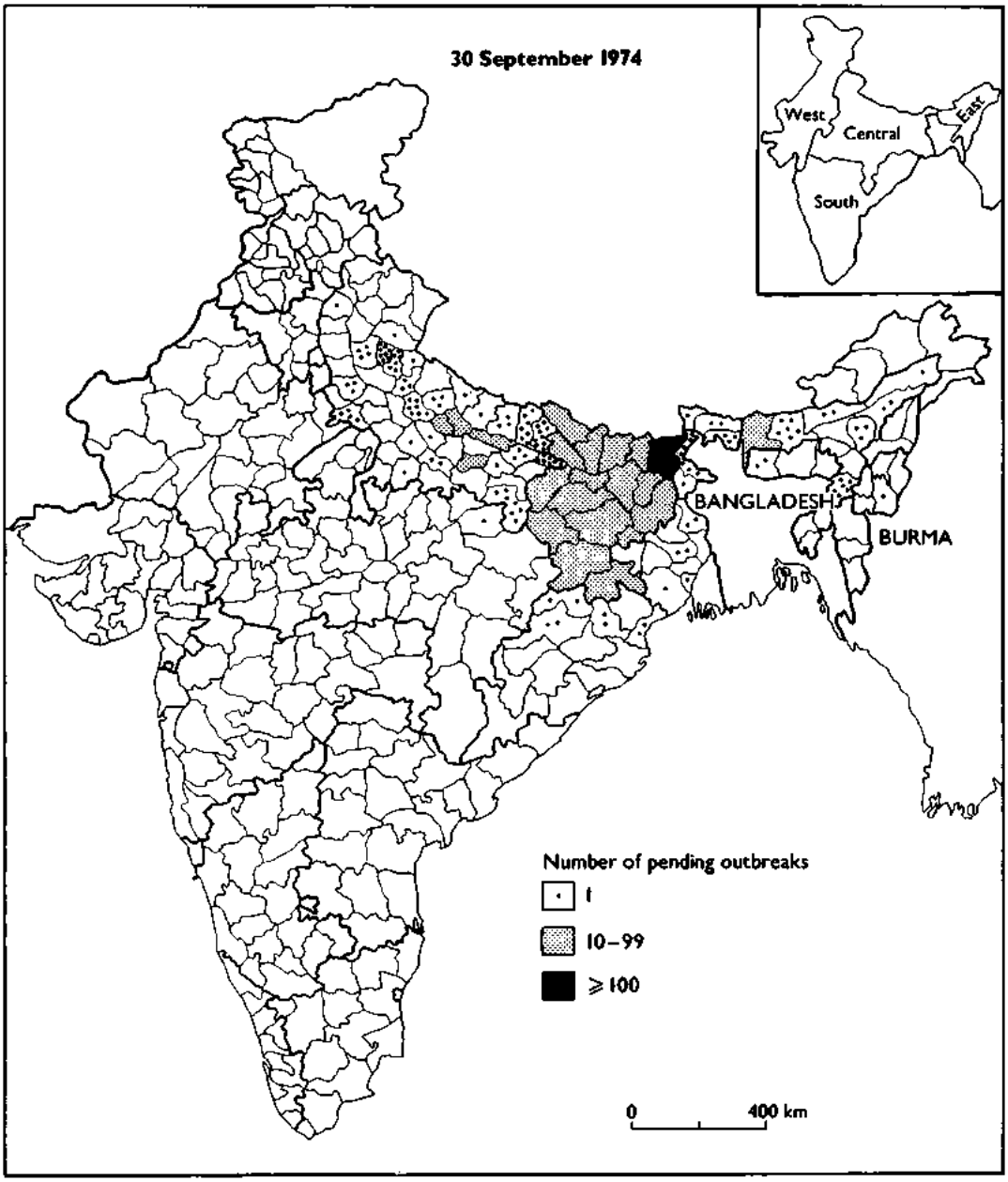


Fig. 15.23. India: number of pending outbreaks of smallpox, by district, as of 30 September 1974.

religious objections to vaccination or feared that patients might be removed to hospital. The offer of a reward had originally been proposed in 1972 in areas with a low incidence of smallpox, but many health officials had been reluctant to adopt the practice, fearing that it would create a precedent with regard to the reporting of cases of other diseases. However, as has previously been described, 5 of the southern states began offering rewards of 10–25 rupees, following the extensive suppression of reports which resulted in the Gulbarga (Mysore) outbreak in 1972. Early in 1974, some other states that had a low incidence or were thought to be smallpox-free also began to offer a reward, which was now increased to 50 rupees. The inducement had not been particularly effective, however, because information about the reward was not widely

Market Searches

Surveys in the traditional weekly markets, held throughout India, were especially useful in detecting cases of smallpox. It was found that 2 searchers could readily question 300–500 market visitors in the course of a working day (Basu & Khodakevich, 1978b) and obtain information about cases in villages 10–20 kilometres distant. It was a technique widely employed by surveillance teams.

Posters showing a smallpox patient and announcing the reward for reporting a case were posted at the entrance to the market and in tea-shops. At each entry point 2 workers were stationed, one of whom asked those entering the market if they knew of cases and which village they were from; the second worker recorded the information. Later, the searchers moved to the tea-shops to continue the questioning. The investigation of all reported or rumoured outbreaks was undertaken the following day.

To assess how effective the market search technique had been, a special study was conducted in a mountainous area of Assam (Khodakevich & Rao, 1978) in January 1976. In a district comprising 695 villages scattered over an area of roughly 15 by 55 kilometres, 7 markets were searched to determine whether outbreaks occurring over the preceding 3 years could be detected. The searchers were health workers who had not been associated with the programme and had no information about previous smallpox in the area. Visitors to the market reported 64 villages as having been infected with smallpox during the preceding 3 years. Investigation revealed that 18 of the villages were in another district, 2 had outbreaks in 1970, 2 had outbreaks of chickenpox, and in 8 others no evidence of outbreaks could be found. The remaining 34 villages in which smallpox was reported to have occurred included all 13 villages which had had outbreaks in 1975, 17 out of 32 of those with outbreaks in 1974 and 4 out of 13 of those with outbreaks in 1973. Although the market searches did not detect all outbreaks, they served to provide a great deal of information at a minimum cost in manpower.

disseminated by the health workers, who wanted to claim the money for themselves. To overcome this problem, it was decided to offer 50 rupees to the person first reporting a previously undiscovered outbreak and 50 rupees to the health worker who received the report.

Containment measures were also strengthened as some surveillance–containment teams, which now had fewer outbreaks to contend with, began to stay in infected villages overnight to ensure that all residents were vaccinated. One or two local inhabitants, termed "watchguards", were hired to stay at each infected house to prevent the patient from leaving and to vaccinate anyone who could not be dissuaded from visiting. Eventually, 4 watchguards were engaged to guard each house with a patient, 2 of them working during the day and 2 at night. This meant that if one watchguard had to absent himself, one would remain on duty. When it was found, in some areas, that visitors avoided the watchguard by entering through a back door, the back entrance was barricaded. Observing that new outbreaks were often found in villages adjacent to those infected, the teams began an increasingly intensive search in a 5-mile (8-kilometre) radius around each infected village.

Information on the means by which outbreaks were actually detected are available for 3798 outbreaks from mid 1973 to mid 1975. The data for the latter half of 1974 and for the first half of 1975 show that an increasing proportion of the outbreaks was being notified by the public and a lesser proportion was detected by periodic search (Table 15.26). In the non-endemic states, notification by the public played a more important role, the proportion of outbreaks so notified increasing from 15% in the first 6 months of 1974 to 29% in the second 6 months and to 36% in 1975.

The outbreaks were detected increasingly earlier after the onset of the first case (Table 15.27), although the standard which called for 75% to be detected within 14 days was never reached. The outbreaks persisted for a shorter time (Table 15.28) but in some of them cases continued to be found more than a month after detection. With earlier detection

Table 15.26. India: methods of detecting outbreaks of smallpox, 1973–1975

Period	Number of outbreaks	Methods of detection							
		Public reports		Regular house-to-house search		Fields visits of health staff		Others[a]	
		Number	%	Number	%	Number	%	Number	%
July–Dec. 1973	457	12	2.6	150	32.8	286	62.6	9	2.0
Jan.–June 1974	2 865	201	7.5	1 729	64.4	742	27.6	13	0.5
July–Dec. 1974	343	33	9.6	160	46.6	147	42.8	3	0.9
Jan.–June 1975	133	15	11.2	57	42.9	39	29.3	22	16.5

[a] Market searches, special searches, cross-notification.

Table 15.27. India: interval between onset of outbreaks of smallpox and their detection, 1973–1975

Period	Number of outbreaks	Interval									
		0–7 days		8–14 days		15–28 days		29–56 days		>56 days	
		Number	%	Number	%	Number	%	Number	%	Number	%
July–Dec. 1973	1 293	303	23	186	14	252	19	230	18	322	25
Jan.–June 1974	6 535	2 170	33	1 724	26	1 605	25	782	12	254	4
July–Dec. 1974	1 369	478	35	248	18	301	22	255	19	87	6
Jan.–June 1975	226	104	46	48	21	45	20	27	12	2	1

Table 15.28. India: interval between onset of first and last case of smallpox, 1973–1975

Period	Number of outbreaks	Interval					
		<1 month		1–2 months		>2 months	
		Number	%	Number	%	Number	%
July–Dec. 1973	1 460	1 065	73	192	13	203	14
Jan.–June 1974	6 559	4 980	76	1 025	16	554	8
July–Dec. 1974	1 234	1 027	83	151	12	55	4
Jan.–June 1975	230	199	87	25	11	6	3

and better containment, the outbreaks, as might be expected, were less extensive (Table 15.29).

Assessment of the ever-more-thorough searches was modified to determine the proportion of villagers who were aware of the reward for reporting cases. It was assumed that if the existence of the reward were generally known, cases would not be hidden for long. Personnel searching for cases were instructed to convey the fact of its existence to all the villagers. Radio, posters, leaflets, rickshaws with loudspeakers and announcements at weekly local markets were also used as a means of information.

During the autumn, the number of pending outbreaks fell steadily, from 2124 at the end of September to 980 at the end of October and to 343 at the end of November (Fig. 15.24), but then the rate of decline slowed considerably. Almost as many new outbreaks were being added to the list as were being removed. The winter season of more rapid transmission had begun. The numbers of outbreaks and cases were at a record low, but, if smallpox transmission was to be interrupted, even more rigorous methods of case detection and containment would be required.

Table 15.29. India: distribution of outbreaks of smallpox by size and year, 1973–1975

Number of cases in outbreak	1973		1974		1975	
	Number	%	Number	%	Number	%
1	34	19	659	33	86	40
2–4	44	25	643	32	86	40
5–9	41	23	348	17	26	12
10–19	31	17	229	11	12	6
20–49	28	16	115	6	5	2
≥50	1	1	19	1	1	1
Total	179	100	2 103	100	216	100

Concern about the programme's progress suddenly turned to alarm in mid-December

Status of the Programme in Early December 1974

Memorandum, dated 9 December 1974, from the Chief of the WHO Smallpox Eradication unit to all smallpox eradication staff:

"The autumn saga of 1974 has been marked by weeks of unexpectedly rapid decreases in the number of pending outbreaks in Asia interspersed with weeks when there has been little or no decline. At present, we seem to be again in the latter phase. Does this signal the beginning of a phase where seasonally increased rates of transmission overbalance our capability to contain the outbreaks *or* does it represent but a pause in the countdown as we regroup to redeploy forces and to tighten up containment procedures and so recommence the countdown? Unquestionably, a greater effort is required during the winter months to ensure containment of each outbreak, but the task can be accomplished.

"With search activities now reasonably well developed in most districts and with market searches and the system of rewards serving to assure discovery of outbreaks missed in search, it seems to me that now is the time to deal far more rigorously with containment measures. In many areas ... staff have not dealt with containment as rigorously as is now required. This is not surprising. During the summer and early autumn months, further spread of smallpox occurred only infrequently even when containment measures were less than optimal. Inevitably, emphasis shifted to improving the search procedures, sometimes perhaps at the expense of the arduous and meticulous work required to assure 100% containment. With increased rates of transmission and more population movement, containment procedures which were effective in October are no longer so.

"At this stage, and with the comparatively few outbreaks we have, *every patient* must be subjected to 24-hour guard and, as required, food provided to the families to provide further incentive for them to stay put. If the guard is fully effective, every subsequent contact will be protected by vaccination. But *frequent* supervision by epidemiologists and senior staff is mandatory if the system is to work. Then begins the now necessary but arduous task of tracing all contacts of the patient from the time of onset of rash. This procedure is in effect in some areas but, as of the time of my visit two weeks ago, it was not in effect everywhere.

"Most important now is for each epidemiologist to consider each new outbreak as being indicative of a possible failure in the system. The question for each outbreak must be asked—'Why did this outbreak occur and what should be done to prevent a repetition of the episode?'"

1974 as major epidemics unexpectedly began in Bangladesh. Catastrophic floods, the worst in 20 years, had swept the northern districts of Bangladesh in August and September and, with the subsequent famine, tens of thousands of refugees migrated to other parts of the country. In December, smallpox began spreading rapidly and once again infected the major cities. The most heavily affected areas were along the northern Bangladeshi–Indian frontier and because of frequent travel across the border, numerous importations were to be anticipated. Of particular concern were the eastern states of India, in which the health services and the smallpox eradication programme itself were the least able to cope.

Realization that a difficult spring might lie ahead was soon followed by the ominous discovery of a cluster of outbreaks at a major pilgrimage site of the Jain religion about 85 kilometres from Patna, the capital of Bihar (Jha & Achari, 1975). The largest outbreak was detected in December 1974 at Puri village, in which the founder of the Jains had died 2500 years earlier. Forty households were infected at the height of the pilgrimage season. Complicating the problem was resistance to vaccination, common among Jains. A special appeal was made to the principal religious leader, who agreed, reluctantly, to recommend vaccination. The entire village was quarantined by the Bihar military police. Twenty-four-hour watchguards were posted at the houses of infected persons and at key areas in the village. A community kitchen was set up to feed patients so they would not have to leave their homes for food. Pilgrims were not allowed to enter sacred pilgrimage

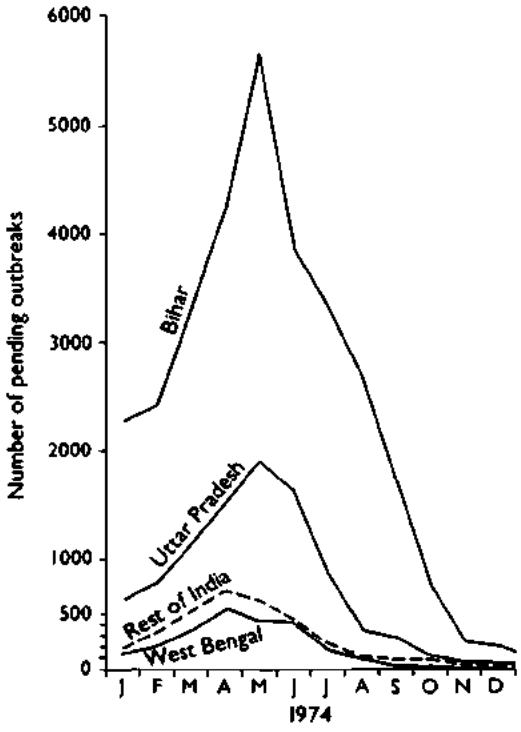


Fig. 15.24. Bihar State, Uttar Pradesh State, West Bengal State and the rest of India: number of pending outbreaks of smallpox at the end of each month, by month, 1974.

areas until they had been vaccinated. Although smallpox spread to 5 adjacent villages, the outbreak in Puri was finally controlled by the end of February 1975.

Elsewhere in the district, the number of outbreaks had increased from 16 to 75. Assessment revealed poorly conducted search operations and inadequate containment. Emergency measures were introduced. Whenever an outbreak was discovered, 20–25 vaccinators were dispatched to the infected village; containment vaccination was completed within 48 hours; 24-hour watchguards were posted at every infected household; and food was brought in to ensure household quarantine. Entire villages were cordoned off when necessary. Instead of a few vaccinators, dozens were assigned to each newly discovered infected village and camped there until no active case remained. In all, 102 new outbreaks were discovered in Bihar in January 1975.

"Operation—Smallpox Zero", January 1975

With smallpox present in only 285 of the more than 575 000 villages of India at the end

Problems in Containment: a Report by a Supervisor in Bihar, May 1975

"We have the misfortune to have to inform you of a new case of smallpox in the Painathi outbreak, a 4-month-old unvaccinated male with onset of rash on 30 April. The household is only 10 metres from a household where a severe case occurred on 13 April.

"The patient and his mother left Painathi on 29 March, 2 days before containment began. The mother was enumerated but the existence of a child was not made known. They returned on 14 April but their presence was concealed by the father. Searchers went daily to each house in the village to vaccinate and to inquire about fever and rash. Dr Khan and Dr Briedert personally visited this house to find out if all the vaccinations were successful and if this woman had returned. The father of the child, however, lied to them.

"The family had been resistant and uncooperative from the start. After enumeration, vaccination was possible only when we climbed over the compound walls and forcibly inoculated each family member. After a rumour reached Dr Khan, who had been staying in the village, he had to use a trick to gain entrance to the house. He asked for a glass of water and this was denied. He knew by custom that they had a case of smallpox inside the house because nothing can be given when a case of smallpox is in the house of a member of this religious sect.

"Dr Briedert is now staying *inside* the infected house. A room-by-room search has been done and will continue daily. All visitors have been traced—all had been previously vaccinated. The mother was vaccinated on 2 May. She has a primary scar and we can only hope that she will not develop into a case. We are nonetheless isolating her and keeping her under close observation for the next 14 days."

Plate 15.16. The search for smallpox cases intensified throughout 1975 as efforts were made to detect all cases of fever accompanied by rash. **A**: A village headman brings a child to smallpox eradication staff for confirmation of diagnosis. **B**: A search worker shows the WHO smallpox recognition card to children. **C**: Posters and writing on a wall advertise a reward of 100 rupees to anyone who detects a case of smallpox.

of December 1974 and with reasonable confidence that there were few undetected outbreaks, it appeared that the elimination of smallpox was at hand. However, from the experience of the past year in Bihar, it was clear that smallpox could spread rapidly in this densely populated area during the winter and early spring. Analysis of the experience in the autumn of 1974 showed that deficiencies in containment were primarily responsible for the failure to stop outbreaks. Vaccination of the population of affected villages was not as rapid as it might have been, visitors to the villages were often not vaccinated and some villages were declared free of smallpox without a thorough follow-up search. Although searches were conducted within a 5-mile (8-kilometre) radius of infected villages, some outbreaks traced to those villages were found to occur at distances of up to 16 kilometres.

At the end of December, new instructions were issued by the government entitled "Operation—Smallpox Zero". The following passages are extracts from the instructions:

"With the outbreaks so few in number, each outbreak must now be dealt with as an *absolute* emergency with maximum mobilization of staff and volunteers. As much concern should be directed to each outbreak as would be directed to control an outbreak in a non-endemic country such as in Europe. *Never* should a case occur more than 21 days after discovery of an outbreak.

"With the very small number of outbreaks present and with fully effective containment, smallpox transmission should be stopped in India in not more than 6–8 weeks. An all-India, all-out effort to achieve this objective will commence immediately and at all levels of the programme. These activities will be conducted under the code name 'Operation—Smallpox Zero' with the objective that no case of smallpox would occur after February.

"*PROCEDURES*

"1.0 A special Central command comprised of senior experienced Government and WHO staff will visit every new outbreak detected after 1 January and will revisit every outbreak in which a case is discovered more than 21 days after its discovery to ensure that every possible measure is being taken. These will supplement, not replace, other supervisory visits. To facilitate this, all new confirmed outbreaks must be reported immediately by cable to the State Programme Officer and to New Delhi. Any case occurring more than 21 days after discovery of an outbreak must similarly be reported by cable.

"2.0 Every outbreak must now be dealt with rapidly and with a massive containment effort. Instead of three or four workers, the containment teams should consist of *15 to 20 workers or more*, headed by the District Medical Officer of Health assisted by a national or WHO epidemiologist. In urban areas, this number may be several times greater. *Vaccination in an infected village/mohalla must be essentially completed within two or at most three days.* Three or four workers must camp in the village/mohalla until all scabs have separated from the last case. Two watchguard-vaccinators must be assigned to each infected house to maintain a 12-hour watch during the day while a second pair maintains a 12-hour watch at night. Watchguards will be responsible for (1) vaccinating all persons visiting the houses of smallpox patients; (2) identifying all household contacts who leave to go to other areas; (3) maintaining isolation of smallpox cases; and (4) maintaining an hour-by-hour log book record of activities and of movement of people in and out of the households. Food, necessary medicines and housing may be supplied to the family of an infected patient on a daily basis to ensure cooperation and isolation. Smallpox containment field books with complete enumeration of the village/mohalla must be completed on each outbreak.

A typical containment team might include:

1. 4 watchguard-vaccinators for each infected house
2. 8 vaccinators of which 4 should camp each night in the village
3. 2 motivation workers (village-level workers who know the village/mohalla and are respected by the villagers)
4. 1 supervisor and 2 vaccinators to trace household contacts who have gone to other areas
5. 3 supervisors
6. 1 containment team leader.

"3.0 House-to-house search will be made in a 10-mile [16-kilometre] radius around an outbreak as well as in high-risk areas which may be outside the 10-mile radius. In the urban areas the surrounding mohallas will be searched in a similar manner. This will be followed in two weeks by a second house-to-house search within a five-mile [8-kilometre] radius to find cases which might have been in the incubation period during the first search.

"4.0 In case of a death, the vaccinator will accompany the remains to be certain that the body is properly disposed of and that all garments are buried. All attending the funeral will be vaccinated, a register of participants and their addresses will be prepared and all villages from which they came placed under surveillance.

"5.0 After 1 January, a laboratory specimen from one or two cases in each new outbreak will be collected."

It was decided that the periodic routine search programmes would consist of house-

to-house visits, whereas previously searchers had checked only a sample of houses in each village. The reward for reporting a case was increased from 50 rupees to 100 rupees. Each suspected case—i.e., one with a rash and fever—was to be recorded in a "rumour register", which was established at every primary health centre. Each patient was to be visited immediately by the local health officer and the diagnosis confirmed by an epidemiologist. If the diagnosis was uncertain, it was to be considered smallpox and watchguards were to be posted. By experience, it was found that good performance on the part of watchguards could be ensured by the simple expedient of not paying them until they were relieved of duty. If, at any time, a watchguard was not found on duty, all 4 were dismissed without pay and new watchguards were recruited. Containment vaccination was to include all persons within a 1-mile (1.6-kilometre) radius of the outbreak. In all, this meant vaccinating some 4000–5000 people in rural areas and 80 000 in urban areas (Sharma & Grasset, 1975). Search throughout an area with a 10-mile (16-kilometre) radius, performed by locally recruited and trained staff, usually encompassed 300–600 villages. The costs of a typical containment operation in 1975 were estimated by Ježek to be about US$2700 (Table 15.30).

Investigations into the source of the outbreak were intensively pursued by national and international epidemiologists, but now, instead of notifying neighbouring states or districts of the existence of a suspected source, they themselves proceeded to the locality. This ensured that the sources would not be missed because of difficulties with telegraphic communication or confusion due to information being received from illiterate villagers and the consequent need to spell village names phonetically.

To guard against importations from Bangladesh, special surveillance teams were assigned and special searches conducted in Muslim Bengali areas and communities in India. Special attention was given to Calcutta, in which repeated night searches were made among the 48 000 street dwellers (Spring, 1975).

Table 15.30. India: estimated manpower employed and costs of a typical containment operation, 1975

		Rupees (Rs.)
1. Substantive staff		
Epidemiologist, 21 days at Rs. 100 per day		2 100
Junior medical officer, 42 days at Rs. 35–50 per day		1 764
Paramedical assistant, 42 days at Rs. 15–30 per day		924
Driver, 102 days at Rs. 10–15 per day		1 224
	Total:	6 012
2. Additional (temporary) staff		
Watchguards (assume 2 infected houses): 8 workers, 42 days at Rs. 5 per day		1 680
Search workers to search 10-mile radius (assume 500 villages), 300 search-days at Rs. 5 per day[a]		1 500
Search workers to do repeat search of 10-mile radius		1 500
Vaccinators to vaccinate the village population (assume 1000 population): 20 vaccinators, 5 days at Rs. 5 per day		500
Vaccinators to vaccinate population in a 1-mile radius: 20 vaccinators, 15 days at Rs. 5 per day		1 500
Supervision (at 1 supervisor to 5 worker–days)		
(a) for search of 10-mile radius, 60 supervisor–days at Rs. 10 per day		600
(b) for repeat search		600
(c) for watchguards, 1 supervisor, 42 days at Rs. 100 per day		420
(d) for vaccinators of village, 4 supervisors, 5 days at Rs. 40 per day		200
(e) for vaccination of population in a 1-mile radius, 4 supervisors, 15 days at Rs. 40 per day		600
	Total:	9 100
3. Petrol		
Usually, each new outbreak was attended by several teams of jeeps for various periods of time. The jeeps were used for supervision, search assessment and follow-up.		
Week 1: 4 jeeps or 28 jeep–days		
Weeks 2–3: 3 jeeps or 42 jeep–days		
Weeks 4–5: 2 jeeps or 28 jeep–days		
Week 6: 1 jeep or 7 jeep–days		
105 jeep–days	Total:	9 450
	Total cost:	24 562 (US$2 730)

[a] Based on petrol costs averaging Rs. 90 per day.

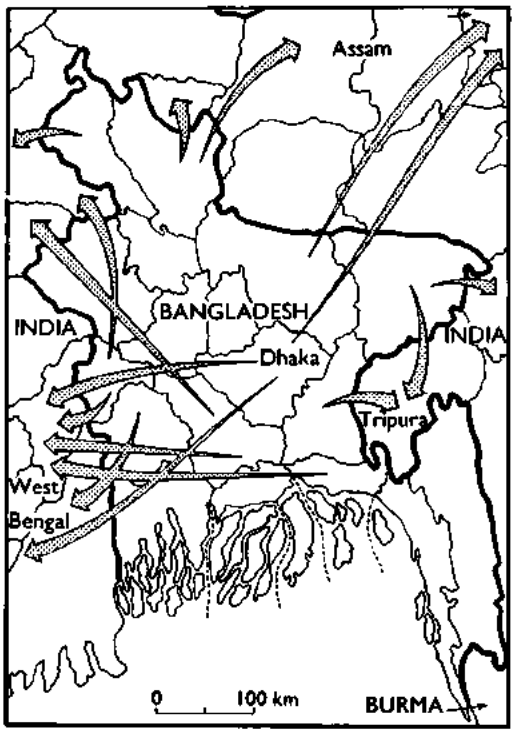


Fig. 15.25. Importations of smallpox from Bangladesh to India, 1975.

"Operation—Smallpox Zero", begun in January 1975, proved to be most successful. From November to December 1974, the number of pending outbreaks had decreased from 343 to 285 (17%); in January, to 194 (32%); and in February, to 113 (42%). As had been feared, cases were imported from Bangladesh, 30 importations being detected in West Bengal, Assam and Tripura (Fig. 15.25). Two-thirds were detected within 2 weeks of the onset of illness in the first case and only 8 additional outbreaks occurred as a result of further spread.

In all, only 308 outbreaks and 1436 cases were detected in India after 1 January 1975 (Tables 15.31 and 15.32). All were in the eastern part of India except for 10 in the far western Kutch desert of Gujarat, introduced by migrants probably infected in Bihar.

In April, 115 000 health workers undertook a week-long, house-to-house search throughout the whole of India. Independent assessment of some 5% of villages showed that 85%–96% of all villages in the various states had been searched. Among 574 517 persons interviewed, 61% knew about the reward for reporting a case and knew the amount of the reward. Only a few

Table 15.31. India: number of reported cases of smallpox, by state and by month, 1975

State[a]	Jan.	Feb.	March	Apr.	May	June	July–Dec.	Total
Assam	29	27	13	18	1	0	0	88
Bihar	654	111	28	25	21	0	0	839
Gujarat	8	2	4	0	2	0	0	16
Meghalaya	25	11	21	4	0	0	0	61
Orissa	0	1	5	0	0	0	0	6
Tripura	0	1	0	1	7	0	0	9
Uttar Pradesh	243	45	5	0	0	0	0	293
West Bengal	51	14	8	33	16	2[b]	0	124
Total	1 010	212	84	81	47	2[b]	0	1 436

[a] Nil reports were received from other states and all the union territories.
[b] The date of onset of the last case was 26 May (cases are listed by month of report).

Table 15.32. India: newly detected outbreaks of smallpox by state and by month, 1975[a]

State	Jan.	Feb.	March	Apr.	May	June–Dec.	Total
Assam	4	3	8	5	1	0	21
Bihar	102	41	9	3	1	0	156
Gujarat	6	0	2	0	2	0	10
Meghalaya	7	10	2	3	0	0	22
Orissa	1	0	0	0	0	0	1
Tripura	0	1	0	1	2	0	4
Uttar Pradesh	44	4	1	0	0	0	49
West Bengal	14	4	9	13	5	0	45
Total	178	63	31	25	11	0	308

[a] Outbreaks were reported immediately by telegraph or telephone; case reports (Table 15.31) were submitted through routine notification channels and were somewhat delayed in receipt.

outbreaks were found, all of which had resulted from importations. Smallpox had been virtually eliminated during the season of most rapid transmission. In May, the last cases and outbreaks in India were discovered.

The Last Case in India, May 1975

As in many other countries, so in India the last case presented some unusual features (Ježek et al., 1978a). Saiban Bibi, a 30-year-old homeless Bangladeshi beggar, developed a rash while living on the Karimganj railway station platform in Assam, where she was begging for food. She had contracted smallpox from a patient in Sylhet District, Bangladesh. On 26 May, she went to the Civil Hospital in Karimganj, which forthwith notified the District Health Officer. Accompanied by a WHO epidemiologist and the state surveillance team, he immediately went to investigate.

The situation was alarming. For the first 4 days of illness, the patient had lived on the platform of the railway station, the gateway to the states of Assam and Tripura and the union territory of Mizoram. Between 22 and 26 May, 9 trains had stopped at the station and 4535 railway tickets had been issued to 68 different towns and cities. A programme was immediately launched to search and vaccinate in the city wards in which the railway station and the Civil Hospital were situated. Later, containment activities extended to the whole town, as well as to all villages visited by the patient since 21 May. Railway authorities were instructed to intensify surveillance activities in and around the railway stations and railway colonies. All district health authorities in Assam and neighbouring states through which the railway passed were asked to initiate intensive searches during the subsequent 14 days. Special searches were conducted in all villages within 10 miles (16 kilometres) of the district border with Bangladesh.

The patient was isolated and 4 watchguards were stationed in the isolation ward for round-the-clock duty. All patients, visitors and hospital staff, together with their relatives, were enumerated and vaccinated. The hospital was closed to visitors and the discharge of patients was stopped. One watchguard was placed at the railway station to carry out surveillance and vaccination.

Three border checkposts were established and all incoming and outgoing travellers were checked and vaccinated. All border security forces and police outposts were alerted to look for possible cases.

Surprisingly, despite the time of year and the many persons who had been in contact with the patient, no further cases were found.

India Celebrates Independence Day and Freedom from Smallpox, August 1975

Six weeks passed after the onset of illness in the last patient and the last outbreak was deleted from the list of pending outbreaks. On 1 July, the reward for reporting a case was increased to 1000 rupees (US$125), the equivalent of 4 months' salary for an Indian labourer. This was done with some trepidation, since it was feared that unscrupulous persons might smuggle smallpox cases from Bangladesh to claim the reward. Indeed, on one occasion this did happen, but the ruse was readily detected. With a reward of this magnitude, thousands of patients with rash and fever were reported to the health authorities. Each was investigated; none proved to have smallpox.

On 15 August 1975—India's Independence Day—the government held a special celebration honouring India's freedom from smallpox, which was attended by the Director-General of WHO.

Less than 3 months had elapsed since the onset of the last case, and with smallpox still present in Bangladesh the staff were understandably apprehensive that at the last moment another focus might be found. The search continued, but an unexpected event of quite another type occurred. On the night of 15 August, the President of Bangladesh was assassinated. The government closed the airports and sealed the borders—to the extent that this was possible. It was feared that there might be yet another mass exodus of refugees.

An emergency surveillance programme was immediately put into operation, focusing on Bengali-speaking areas. Possible migration routes were identified, dozens of surveillance posts were set up at border crossings, special searches were conducted in designated high-risk areas and surveillance was intensified in Calcutta. Happily, the refugees were few and no further importations occurred.

On 16 October 1975, the last case of smallpox occurred in Bangladesh and the 2-year search began to confirm eradication throughout Asia.

Why the Smallpox Eradication Programme Succeeded

Two papers have been published by members of the smallpox eradication staff which comment on distinctive features of the smallpox eradication programme in India that were crucial to its success. Extracts are given below:

"The strategy used and the manpower and other resources provided ... greatly contributed to the rapid success of the programme; but without the passion given to the planning and implementation of the programme by the workers, achievement would not have been possible. Jawahar Lal Nehru once said 'Planning would be meaningless unless behind the plan there was a passion—passion with a tinge of anger at delays, anger at anybody not doing his part, anger at not achieving where achievement is possible'. The national and WHO staff have fought with passion the battle against smallpox... Hundreds of men and women—nationals and internationals—have worked up to 18 hours a day for seven days a week in the belief of an ideal which they have put above their personal happiness, their family life, their career and their health. The central level staff both of the WHO and the Government of India have spent on an average three weeks a month working in the field throughout the country to train, motivate, encourage the local staff. During the 1974 summer epidemic of smallpox in Bihar and [Uttar Pradesh], a number of WHO, central and state officers were publicly laughed at for having predicted that their states and the country would be free of smallpox in less than a year... Men and women from different states in India and from many countries of the world put aside their racial, national, religious or social prejudices and bore together all the difficulties and hazards. Many took risks in putting aside conservative regulations, red tape and antiquated technical methodologies, when these threatened to delay their task or obstruct the path to success. The toughest of men and women on many occasions were on the verge of discouragement—from physical tiredness and mental frustration, when having to cope with hundreds of infected villages in their area of responsibility. They persevered, waiting days, weeks, sometimes months, until it was possible to send them more men, better vehicles, funds for petrol, etc. In the smallpox offices in New Delhi and also in the state, district and block headquarters, medical officers, administrators and secretarial staff worked most of the days far into the night, over the weekends and public holidays so as to make sure that those in the field received the necessary support. However, even during the most difficult stages of the programme, men and women in the field and offices discovered like Rabindra Nath Tagore that they 'acted and behold duty was joy'." (Sharma & Grasset, 1975.)

"The decentralisation of authority to implement the strategy to the district health authorities and epidemiologists who were responsible for proper utilisation of available resources resulted in the early detection and effective containment of large numbers of disease foci in the shortest possible time and the consequent quick interruption of transmission. If one considers that ... India ... [was] spending over 40 million rupees a year for the past ten years on NSEP and [that an] additional amount of about Rs. 20 million each [year was being spent by WHO] during the campaign years 1973–74 and 1974–75... it becomes apparent that it has not been the quantum of money spent but the manner of doing it which made all the difference between success and failure. Relative freedom at district levels to take on-the-spot decisions to spend this additional amount... greatly contributed to the realisation of smallpox free status. Administrative and operational restraints in implementing the strategy were also minimal.

"All the national health programmes have built-in evaluation methods. The interval between occurrence of a defect/problem and its detection and the interval between the detection and correction has always been considerable... In this smallpox campaign the continuous monitoring of the smallpox status, feedback from the field staff and the authority for taking on-the-spot decisions regarding fiscal, administrative and technical matters have narrowed down the unknown and the unsolved problems to the minimum." (Dutta et al., 1975.)

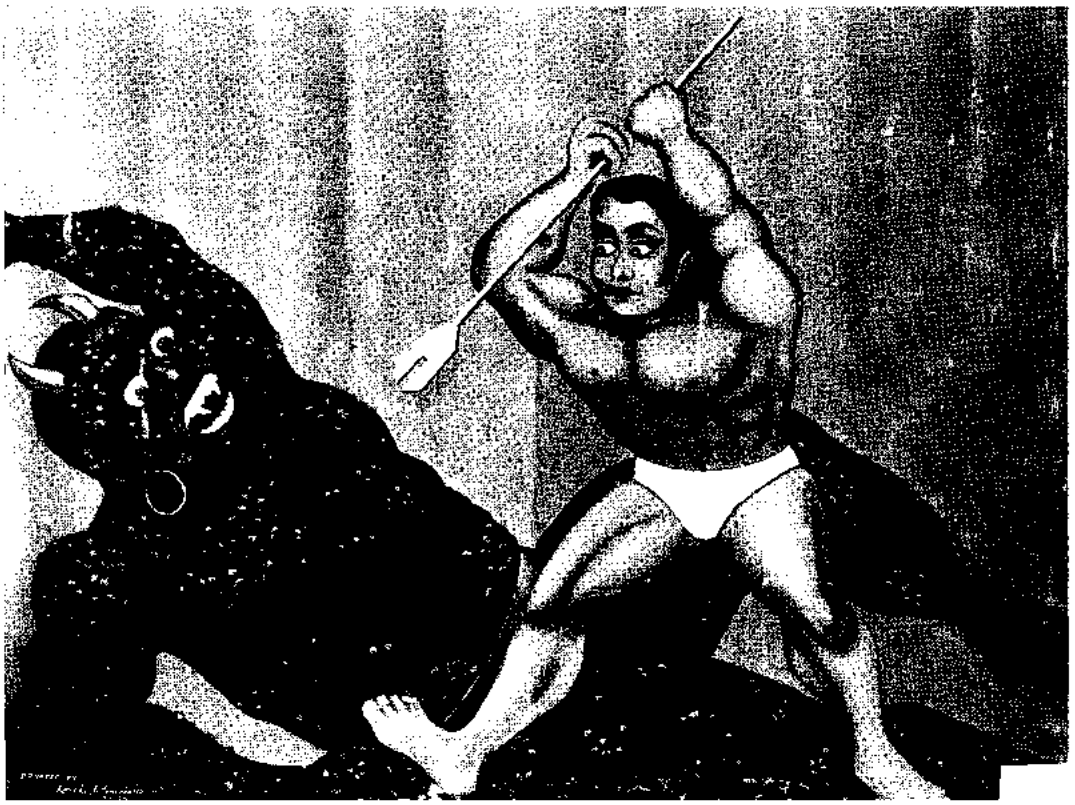


Plate 15.17. A wall-sized poster, in the style of a cinema advertisement, depicts a hero slaying the smallpox demon with a bifurcated needle. This poster, also used in smaller sizes, was displayed widely in India to promote the reward for reporting a case of smallpox.

Morbidity and Mortality Data

Information regarding the age, sex, vaccination status and survival or death of the patient was obtained for all cases in India. However, data were tabulated nationally for only a proportion of the total for the years 1974–1975 (Basu et al., 1979). These data were obtained from 4 high-incidence states and 13 low-incidence states and union territories, although most of the cases were from the former group. The age distribution of cases and case-fatality rates were similar to those observed elsewhere in the Asian subcontinent (Table 15.33).

Data are available for 23 546 of the 189 439 cases which occurred in 1974–1975. In all, 31% occurred in individuals less than 5 years of age, 40% in those aged 5–14 years, and 29% in those aged 15 years and over. The disease was equally prevalent among males and females.

A similar distribution of cases by age and sex was observed in all states with a high incidence. Imported cases in smallpox-free states, however, occurred predominantly in males (64.6%) in the older age groups, 18.7% being in men aged 50 years and over. This was attributed to the occurrence of many cases among migrant labourers and pilgrims, a much larger proportion of whom were adult males.

Data regarding the vaccination status of 14 463 cases from the same 17 states and union territories reveal that two-thirds of the persons concerned were unvaccinated (Table 15.34). Patients were classified as "unvaccinated" if they had no vaccination scar (regardless of whether they claimed to have been vaccinated) or if they had been vaccinated during the incubation period of the disease, too late to prevent infection.

The proportion of cases among individuals with an apparent vaccination scar was markedly higher than in other countries. This is explained by the frequent occurrence of vaccination-like scars associated with the use of rotary lancets in which secondary bacterial

Table 15.33. India: number of reported cases of and deaths from smallpox and case-fatality rate in 17 states and union territories, by age group, 1974–1975[a,b]

Age group (years)	Cases		Deaths		Case-fatality rate (%)
	Number	%	Number	%	
<1	1 373	5.8	597	14.5	43.5
1–4	5 867	24.9	1 436	35.0	24.5
5–9	5 875	24.9	783	19.0	13.3
10–14	3 626	15.5	308	7.5	8.5
15–19	1 916	8.2	124	3.1	6.5
20–29	2 462	10.6	369	9.1	14.9
30–39	1 320	5.6	192	4.7	14.4
40–49	695	2.7	140	3.4	20.1
⩾50	412	1.8	154	3.7	37.4
Total	23 546	100.0	4 103	100.0	17.4

[a] From Basu et al. (1979).
[b] States with a high incidence: Bihar, Madhya Pradesh, Uttar Pradesh and West Bengal. Others: Andhra Pradesh, Assam, Gujarat, Haryana, Jammu and Kashmir, Karnataka, Maharashtra, Orissa, Punjab, Rajasthan, Tamil Nadu, Tripura, and the union territory of Delhi.

Table 15.34. India: vaccination status of cases of smallpox in 17 states and union territories, by age group, 1974–1975

Age group (years)	Vaccinated		Unvaccinated		Total
	Number	%	Number	%	
0–4	506	12.1	3 671	87.9	4 177
5–9	1 008	26.7	2 767	73.3	3 775
10–14	933	41.0	1 343	59.0	2 276
15–19	490	41.8	683	58.2	1 173
20–29	725	49.5	739	50.5	1 464
30–39	549	65.2	293	34.8	842
40–49	281	71.9	110	28.1	391
⩾50	275	75.3	90	24.7	365
Total	4 767	32.9	9 696	67.0	14 463

infections occurred but vaccinia virus did not grow. Most of the cases among "vaccinated" children under 5 years of age occurred in Bihar and Madhya Pradesh, in which, as late as 1973, rotary lancets were still being used in some areas, especially the large municipalities. In Andhra Pradesh, in which the use of rotary lancets was abandoned in 1969, only 15.4% of cases occurred among those with what appeared to be a vaccination scar.

Case-fatality rates in India varied from 21% to 31% during 1950–1967 but for most years they were in the range of 25–30%. During the course of the eradication programme, the case-fatality rate dropped steadily, from 31.2% in 1967 to 16.6% in 1974 and to 12.3% in 1975 (Fig. 15.26). The decline is accounted for by an increasing completeness of the notification of cases. Initially, most cases and deaths were reported from infectious disease hospitals, to which the more seriously ill were taken and which recorded high case-fatality rates. As time progressed, differences between case-fatality rates in the various states narrowed considerably. Moreover, a much higher proportion of cases in otherwise smallpox-free areas was found among older children and adults, who experienced a lower case-fatality rate than did young children. Data for 23 546 cases that occurred in 1974–1975 show an overall case-fatality rate of 17.4%, but among infants under 1 year of age the rate was 43.5% whereas it was only 6.5% among the 15–19-year-olds. Although wide variations in case-fatality rates were observed in different epidemics, these variations were considered to be due to differences in the age distribution of the cases, the nutritional status of patients, and the history of previous vaccination.

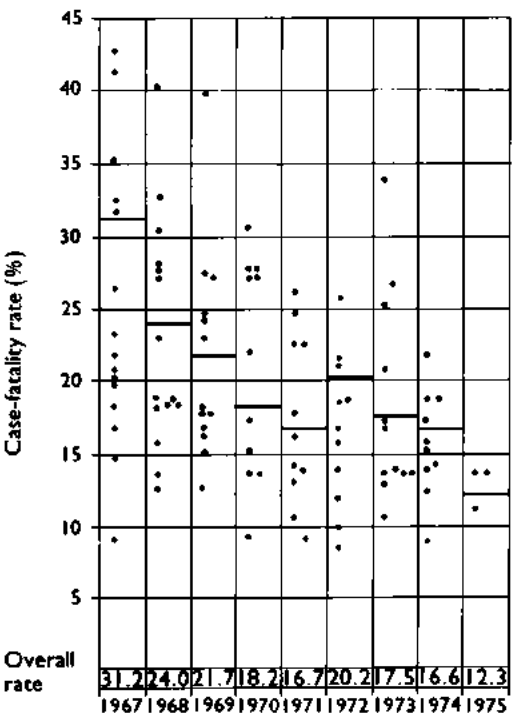


Fig. 15.26. Case-fatality rates for India and the states of Andhra Pradesh, Assam, Bihar, Gujarat, Haryana, Jammu and Kashmir, Karnataka, Madhya Pradesh, Maharashtra, Orissa, Punjab, Rajasthan, Tamil Nadu, Tripura, Uttar Pradesh and West Bengal, by year, 1967–1975. Each dot represents the case-fatality rate in a state in a year. For each year rates are plotted only for the states that recorded at least 100 cases that year. The bold lines denote the overall rate for India in the year shown.

NEPAL

Introduction

Epidemiologically, Nepal was a mountainous extension of the Indian states of Bihar and central and eastern Uttar Pradesh, but its programme differed significantly from that in India. Of the country's 10.8 million population (in 1967), 37% lived in the Terai, a northern strip of the broad Ganges river plain (see Fig. 15.1), which in Nepal was about 25–35 kilometres wide; another 53% lived in the adjacent Middle Hills area, which ranged from 30 to 50 kilometres in width. Most of Nepal's population thus lived within some 80 kilometres of the border with India and the majority were Hindu. Many had relatives in adjacent areas of India, and travellers and migrant labourers moved freely across the border. Roads were few, communications were difficult and the health services and other governmental structures were in an early phase of development.

In 1962, a WHO nurse working in Nepal assisted in the development of a pilot mass vaccination campaign in the Kathmandu valley, comprising 3 of Nepal's 75 districts with a population of 500 000. In 1968, the campaign was extended to other districts and by 1973 it included the entire country. Little was done to develop a reporting system until 1971. Data prior to this time represent only a partial enumeration of cases in the Kathmandu valley.

Strategically, the programme in Nepal was initially not of high priority in the global strategy because eradication there depended on the progress of the campaign in India, particularly in Bihar and Uttar Pradesh. Moreover, the mainly mountainous terrain, the predominantly rural population and the poor communications between villages in Nepal suggested that smallpox transmission could not be long sustained in most of the country. Since the population of the Terai was only about 4 million—the equivalent of 2 districts of India—it was expected that the interruption of transmission in that area and in the country as a whole would not constitute a major problem once smallpox had been controlled in India.

Because the health structure in Nepal was rudimentary and vaccine was available to only a small proportion of the population, additional WHO support was provided from 1968. The eradication programme was intended to make vaccination more widely available initially in the most populous areas along the border with India. Three years later, a plan was implemented to extend reporting and surveillance–containment measures progressively throughout the 75 districts. Progress in achieving these goals was remarkably rapid: by 1972 each outbreak was being investigated and contained and its source identified. Continuing transmission was, in fact, largely stopped in that year. Epidemic smallpox in the neighbouring Indian states of Bihar and Uttar Pradesh, however, resulted in an additional 239 outbreaks in 1972 and 1921 cases during the period 1973–1975. Most of these outbreaks could be traced directly or indirectly to importations and although they sometimes remained undetected for many weeks and were not always well contained, smallpox did not usually spread widely. On 6 April 1975, the last known case of smallpox occurred in Nepal as a consequence of an outbreak resulting from an importation from Bihar.

The Country: Geographical and Sociocultural Considerations

Until 1951 Nepal, ruled by hereditary prime ministers, had been closed to the outside world, and no organized health services or educational facilities existed. When a constitutional monarchy was instituted in 1951, Nepal began the arduous task of building a transport, communication, health and educational infrastructure. Because of the mountainous nature of the country and the dearth of human and natural resources, progress was slow. Throughout the 1970s, Nepal remained one of the world's least developed countries.

Administratively, the country was divided into 14 zones, which were subdivided into 75 districts; the population of a district ranged from 7000 to 350 000, a far smaller figure than that for a district in India. The smallest administrative unit was the panchayat, of which there were some 4000.

Until the 1960s smallpox had occurred widely throughout Nepal. According to a health survey conducted in 1965–1966, 24% of people over 30 years of age in the capital city of Kathmandu bore the facial pockmarks of smallpox, as did 13% of those aged 10–29 years and 6% of children under 10 (WHO/SE/78.107, Shrestha). Variolation

was known to have been widely practised until recent years and many older persons bore the resulting scars. However, unlike the situation in Afghanistan (see Chapter 14), the practice had died out in Nepal by the time the Intensified Smallpox Eradication Programme began. No cases attributable to variolation were discovered during the course of the programme.

As in India, smallpox epidemics were reported to have occurred approximately every 5 years, the last having happened in 1958 (WHO/SE/78.107, Shrestha). However, up to 1963, there was no reporting system; indeed, until 1971 few reports were received from anywhere except the small districts comprising the Kathmandu valley, the site of the capital city. Some Nepalese, especially those living in the Terai, had been vaccinated in India, as had some living near Kathmandu or in the vicinity of the few health units that had vaccine. Otherwise, vaccination was little practised in Nepal.

Socio-economic and demographic factors played unusually important roles in the development of the programme and in the pattern of occurrence of the disease. Geographically, the country consisted of three horizontal belts (Fig. 15.27) extending across the country: the flat Terai of the Ganges river plain, with a population density ranging from 750 per square kilometre in the east to fewer than 100 per square kilometre in the less fertile west (Fig. 15.28); the Middle Hills area, with a terrain rising as high as 3000 metres and containing a few broad populous valleys including the Kathmandu valley, which had a population density of almost 1000 per square kilometre and about 5% of the country's inhabitants; and the Himalayan mountains, comprising 30% of the land surface but containing only 5% of the population. Very few people crossed the Nepal–China border, but travel across the Nepal–India border was unimpeded and frequent.

With only 680 kilometres of paved roads and 2 short railway lines (Fig. 15.27), there was little easy communication between the different areas of Nepal, although a network of footpaths connected the 29 000 villages and market centres in which 95% of the population resided. Kathmandu (population in 1971, 150 000) and Biratnagar (population, 45 000) were the only significant urban centres. On the other hand, contacts between the Terai and Kathmandu and India were numerous and were facilitated by the few motorable roads between the two countries.

The Nepalese of the Terai are Hindu and ethnically similar to their Indian neighbours. Many resisted vaccination for religious reasons; temples to Sītalā mata, the goddess of smallpox, were to be found throughout the

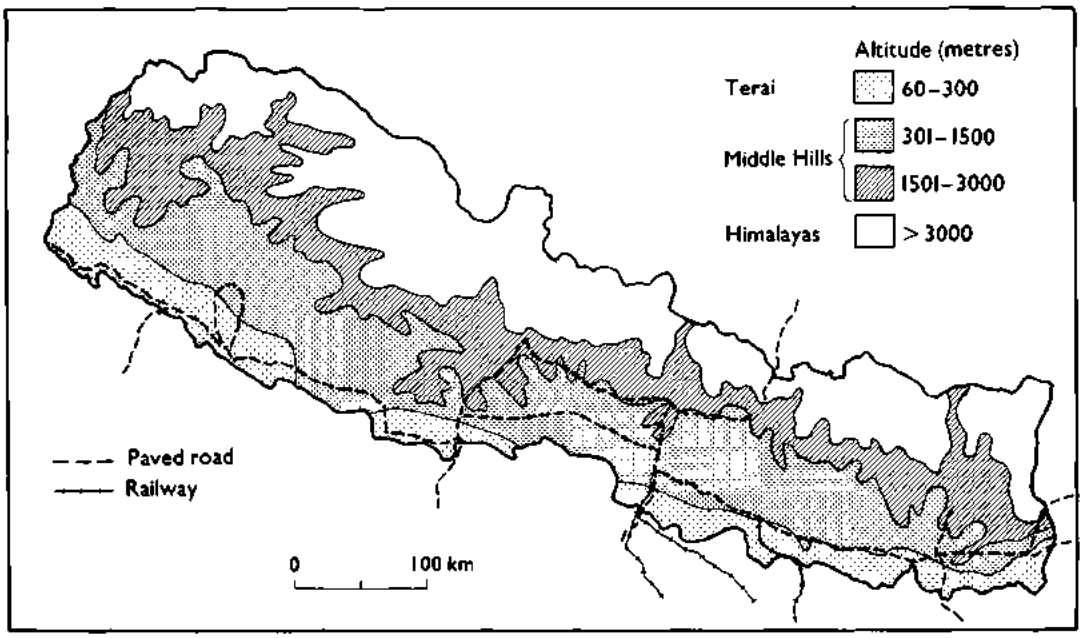


Fig. 15.27. Nepal: physical topography, showing paved roads and railways.

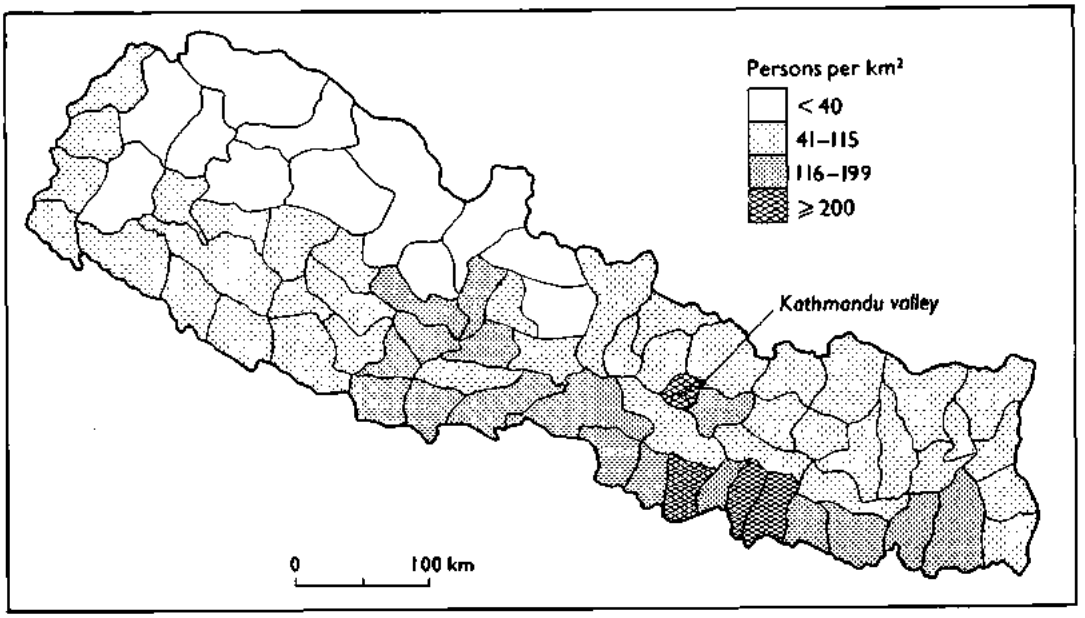


Fig. 15.28. Nepal: population density, by district.

region. The relatively rich agricultural and industrial area of the eastern Terai attracted numerous Bihari and Bengali seasonal migrants, who formed a sizeable proportion of the labour force. Travel to and from the less prosperous western Terai was limited primarily to family visits, and few travelled long distances. Those living in the Middle Hills were predominantly Hindu, but with the exception of some segments of the Newar ethnic group in the Kathmandu valley most people readily accepted vaccination. Travel to and from the Middle Hills was less frequent than within the Terai, although many moved to the Terai and to India for the winter months. Numerous inhabitants of the Eastern Hills worked on tea estates and as forest labourers in the Indian state of Assam and those in the Western Hills travelled to western Uttar Pradesh and cities of western India for work and trade. In the sparsely populated Himalayas, villages were isolated. To reach most districts from the endemic areas of India required a trek of more than 14 days—longer than the incubation period of smallpox. Because of these factors, smallpox proved to be primarily a problem of the Terai, only 4 outbreaks ever being detected in the extensive northern mountainous areas (SME/77.1, Shrestha et al.).

J.S. FRIEDMAN

Plate 15.18. At times, the roads in Nepal were almost impassable.

A Smallpox Control Pilot Project Begins, 1962

A smallpox control pilot project was initiated in 1962 in the 3 districts comprising the Kathmandu valley, which had a population of about 500 000 at that time (WHO/SE/69.10, Singh). With assistance provided by a WHO nurse already employed in another project in Nepal, a house-to-house mass vaccination campaign was begun, utiliz-

ing the multiple pressure method of vaccination and freeze-dried vaccine provided by WHO. As in India, all records were maintained in family registers in which the names of all residents of households were laboriously compiled, revised and updated. The programme was poorly funded, poorly supervised and poorly executed and with the additional impediment of resistance to vaccination progress was slow. A sample survey carried out late in 1964, 2½ years after the programme began, revealed that only 31% of the population had vaccination scars. In 1963, for the first time Nepal began to report cases of smallpox to WHO, but virtually all of them had occurred within the city of Kathmandu. In 1966, a WHO medical officer was assigned to assist the programme, but no effort was made to develop a national reporting system, and until 1968 the programme remained what it had been—an ineffective vaccination campaign confined to the Kathmandu valley. Repeat surveys in May 1967, conducted among various population groups in that area, showed that only 40–65% of the people examined had vaccination scars or the pockmarks of smallpox (WHO/SE/69.10, Singh).

The Programme Extends Beyond the Kathmandu Valley, 1968

In 1967 the government and WHO agreed on a phased plan to extend the programme zone by zone throughout the country. This commenced the following year with the hope that the last of the zones would be included in the programme by 1972. Additional resources were made available by the government, and WHO provided support in the form of personnel, vehicles and equipment and also covered the cost of petrol (Table 15.35). Staff were recruited, trained and assigned to district offices to serve as "senior vaccinators". During the first 3 months of a new vaccination campaign in a district, temporary vaccinators were hired to vaccinate widely throughout the district. Subsequent vaccination and surveillance were then the responsibility of the senior vaccinator. The family registers were abandoned and multiple puncture vaccination with bifurcated needles was introduced.

The number of districts covered by the programme grew from 3 in 1967 to 15 in 1968 and to 41 by the end of 1970. The number of vaccinations performed increased 10-fold, from 201 000 in 1965–1966 to 2 196 000 in 1968–1969 and to 2 823 000 in 1970–1971 (Table 15.36).

Community leaders and such health staff as were available were contacted and requested to report cases, but the numbers of cases notified remained few: 110 cases were reported in 1967, 249 in 1968, 163 in 1969 and 76 in 1970 (Table 15.37). Although reporting was very incomplete, it is probable that the true incidence in Nepal during these years was not high because the corresponding

Table 15.35. Nepal: financial inputs by the government of Nepal and WHO for smallpox eradication, 1962–1976 (US$)[a,b]

Year	Government of Nepal	WHO	Total
1962	2 447	–	2 447
1963	3 598	–	3 598
1964	4 702	–	4 702
1965	5 334	–	5 334
1966	6 000[c]	17 828	23 828[c]
1967	31 000[c]	68 875	99 875[c]
1968	53 615	100 590	154 205
1969	64 334	64 414	128 748
1970	82 400	6 589	198 989
1971	121 071	122 404	243 475
1972	147 339	158 629	305 968
1973	165 000	166 554	331 554
1974	163 500	94 993	258 493
1975	158 262	160 346	318 608
1976	169 343	129 815	299 158
Total	1 177 945	1 201 037	2 378 982

[a] Based on WHO financial records and data from the government of Nepal (SME/77.1, Shrestha et al.).
[b] Excluding the cost of 160 000 vials of vaccine.
[c] Estimated.

Table 15.36. Nepal: number of vaccinations performed, 1962–1976

Year	Total number of vaccinations	Number of primary vaccinations[a]	Percentage of primary vaccinations[a]
1962–1963	218 025	. .	. .
1963–1964	69 107	. .	. .
1964–1965	160 796	. .	. .
1965–1966	201 243	. .	. .
1966–1967	643 699	. .	. .
1967–1968	1 246 033	13 698	1.1
1968–1969	2 195 942	282 613	12.9
1969–1970	2 136 468	521 571	24.4
1970–1971	2 823 098	503 462	17.8
1971–1972	6 162 478	598 958	9.7
1972–1973	6 516 395	991 860	15.2
1973–1974	6 418 402	1 049 405	16.3
1974–1975	6 187 076	367 470	5.9
1975–1976	5 694 195	604 240	10.6

[a] . . = data not recorded.

Table 15.37. Nepal: reported number of cases of smallpox, by districts reporting cases, 1963–1975

Year	Number of cases	Number of districts in the programme	Number of districts reporting cases
1963	1 105	3	3
1964	135	3	3
1965	70	3	3
1966	164	3	3
1967	110	3	3
1968	249	15	8
1969	163	29	7
1970	76	41	1
1971	215	50	6
1972	399	58	9
1973	277	75	18
1974	1 549	75	28
1975	95	75	2

incidence in the neighbouring Indian states of Bihar and Uttar Pradesh was low.

The Programme Strategy Changes, 1971

Early in 1971, a new strategy, unique to Nepal, was adopted and effectively executed by an energetic Nepalese programme director, Dr P. N. Shrestha, and an experienced WHO smallpox adviser, Dr M. Sathianathan, from Sri Lanka, assisted by 2 United States technical officers—veterans of the western Africa programme—Mr Jay Friedman and Mr David Bassett. It was decided to extend the programme as soon as possible to cover the entire country. Forty-five Nepalese district supervisors were recruited and assigned to most districts in the Terai and Middle Hills, and assistant supervisors or senior vaccinators were sent to the other 30 districts, where each worked under the direction of one of the district supervisors. A senior supervisor was responsible for managing the programme in each of Nepal's 14 zones. In 6 districts, responsibility for smallpox eradication was assigned to a newly planned integrated health services project office (Fig. 15.29).

WHO and Nepalese staff decided that the vaccination campaign would be conducted during a single month in the winter of each year, and for this purpose temporary vaccinators (1 for each panchayat, comprising about 3000 persons) were recruited and trained during a 3-day training session. Simple tally sheets replaced the more elaborate record forms. During the remaining 11 months of the year, the assigned permanent smallpox eradication staff, numbering in all

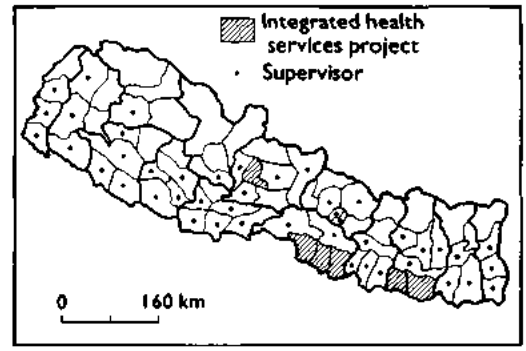


Fig. 15.29. Nepal: administrative divisions and location of district supervisors, 1971.

about 600 persons, travelled from village to village throughout the districts seeking information about smallpox from local leaders, schoolteachers and the personnel of health units. When cases were discovered, the staff were responsible for containment. Four central containment teams were formed to assist in this effort but were soon disbanded, since it proved impossible for them to reach the site of an outbreak before several days—or even weeks—had elapsed because of problems of communication and travel.

Despite the fact that mass vaccination was conducted during the course of a single month each year, the number of reported vaccinations increased to more than 6 million in 1971–1972—a number equivalent to 50% or more of the population—and continued at this level over the next 5 years. Surveys of vaccinial immunity, conducted in 1975 in many of the more accessible areas, revealed that in most of these areas more than 95% of the population bore vaccination scars.

Reporting improved as the programme extended its operations; by early 1973 weekly telegraphic reports were being received from each district regardless of whether any cases had occurred.

Because of the difficulties of travel, responsible district supervisors proved to be the vital element in the programme. They were brought to Kathmandu annually for refresher training and were visited as often as possible in the field by Nepalese and WHO staff, who, beginning in 1972, undertook to visit the site of each outbreak to assess the efficacy of the containment measures. To facilitate travel to the most remote districts, arrangements were made by WHO to permit the charter of a helicopter; it was used on perhaps a dozen occasions during the subsequent 3 years.

Plate 15.19. **A**: Purushollam N. Shrestha (b. 1939), the director of the smallpox eradication programme in Nepal from 1971. **B**: Jay S. Friedman (b. 1940), a WHO technical officer, being presented with a certificate of appreciation by the Prime Minister of Nepal, Tulsi Giri.

In 1972, the programme was extended to include all districts in the Terai and Middle Hills—the districts of greatest concern. Because of the isolation of the villages, most outbreaks were readily contained, and by the end of June 1972, transmission appeared to have been interrupted. During the last 6 months of the year, only 5 outbreaks, with 34 cases, were discovered (WHO/SE/74.71, Shrestha et al.); 4 resulted from importations from Uttar Pradesh and 1 from Bangladesh, whose north-western border with India was less than 50 kilometres—merely a day's journey—from Nepal.

However, as epidemic smallpox swept across Uttar Pradesh and Bihar in 1973, increasing numbers of cases began to be imported into Nepal (Fig. 15.30). In all, 43 outbreaks and 277 cases were reported that year, of which 35 outbreaks resulted from importations from India. Twenty-eight more cases occurred in these outbreaks that were not officially notified until 1974. Most of the imported cases had been infected in bordering districts of Uttar Pradesh and Bihar. The sources of the outbreaks included 12 districts in Uttar Pradesh and 9 in Bihar. One infected traveller came from the state of Maharashtra, although he was probably infected while travelling through Uttar Pradesh. All but 4 of the importations occurred in districts bordering on India.

Smallpox did not spread extensively, however. From the 35 importations, secondary spread to other villages occurred on only 7 occasions, one of these villages being the source of a further outbreak. The number of cases in each outbreak ranged from 1 to 38 with a mean of 8.3 cases, of which almost one-third (13 out of 43) were single-case outbreaks (Table 15.38).

In November and December 1973, the number of importations began to increase

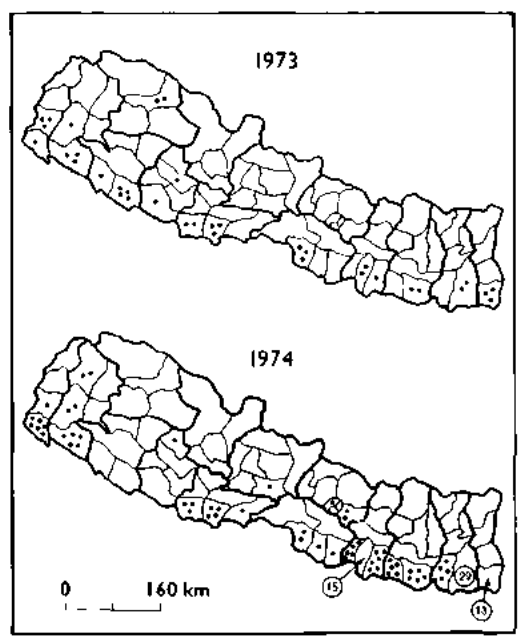


Fig. 15.30. Nepal: importations of smallpox, 1973 and 1974. Each dot denotes one outbreak.

Table 15.38. Nepal: number of outbreaks of smallpox, by number of cases in each outbreak, 1973–1975

Year	Total number of outbreaks	Number of cases in each outbreak					
		1	2–4	5–8	9–15	16–20	≥21
1973	43	13	8	7	5	4	6
1974	180	42	54	27	24	15	18
1975	16	7	4	2	0	1	2
Total	239[a]	63	65	36	29	21	25

[a] Data for 28 outbreaks not available.

and in January 1974, 14 importations were detected, of which 8 were from Bihar and 6 from Uttar Pradesh (Fig. 15.31). The number rapidly increased during May and then abruptly diminished, which was consistent with the seasonal decline in smallpox. In all, 180 outbreaks and 1549 cases occurred, of which 115 outbreaks were due to importations. As was the case in 1973, most of them (106 out of 115) occurred in districts bordering on India, the eastern districts of the Terai being the most heavily infected. In contrast to 1973, when the sources of infection were widely dispersed geographically, 68% of all importations during 1974 came from 5 heavily infected districts in Bihar. These districts, besides being among the most heavily infected in India, experienced severe food shortages in the spring of 1974 and, in consequence, many people migrated to Nepal.

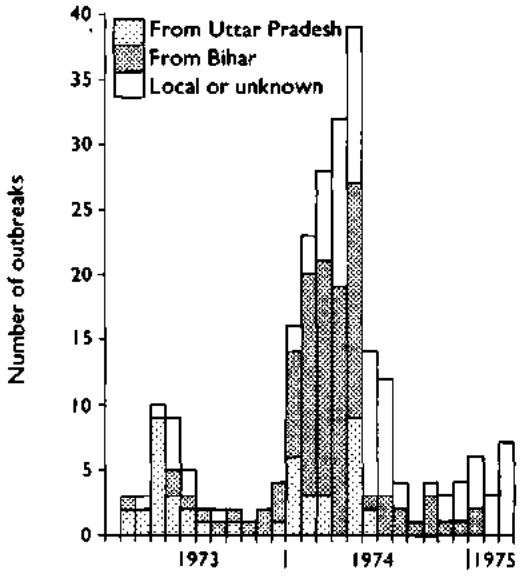


Fig. 15.31. Nepal: number of outbreaks of smallpox, by source, by month, 1973–1975.

In early 1974, WHO arranged for the prompt, reciprocal cross-notification by telegram between India and Nepal of possible sources of infection in each country. Programme staff agreed to investigate every report of this kind and to confirm whether an outbreak had been found. Nepalese staff fulfilled this responsibility well and detected a number of outbreaks not previously known. In India, especially in Bihar, the system operated far less well: with numerous outbreaks and a poorly organized health system, many reports were ignored (WHO/SE/74.71, Shrestha et al.).

The increase in the number of outbreaks in Nepal taxed the resources for surveillance and containment, and a greater number of outbreaks began to result from local spread. Nineteen out of 57 such outbreaks (167 cases) occurred between February and September following 2 importations into the Kathmandu valley. Most were in the Newar ethnic group, who had resisted vaccination for religious reasons, and among whom it was a common practice for the relatives and friends to visit those who were ill with smallpox. Detection was also difficult because families did not report cases and sometimes hid the patients from health officials. Smallpox could therefore spread widely and containment was difficult.

A second problem area was in the western Terai, in which another ethnic group who also resisted vaccination had the custom of granting any wish to a child with smallpox in the belief that the child was possessed by the goddess of smallpox, Sītalā mata. The child's wish was frequently to be taken to see relatives or friends in other villages. In this area, smallpox spread unusually rapidly among groups of villages (SME/77.1, Shrestha et al.).

A third area which proved difficult was a south-eastern district, Morang, which experienced 29 importations in 1974 and 1 in 1975. It was the centre of jute production in the eastern Terai and contained the industrial town of Biratnagar. Numerous migrant labourers from India were attracted to the area and, in the autumn of 1974, because of food shortages in Bihar, many beggars from India arrived there. Quite a few of the migrant labourers and most of the beggars belonged to a tribal group which worshipped Sītalā mata and resisted vaccination (SME/77.1, Shrestha et al.). The last chains of transmission began in December 1974 and

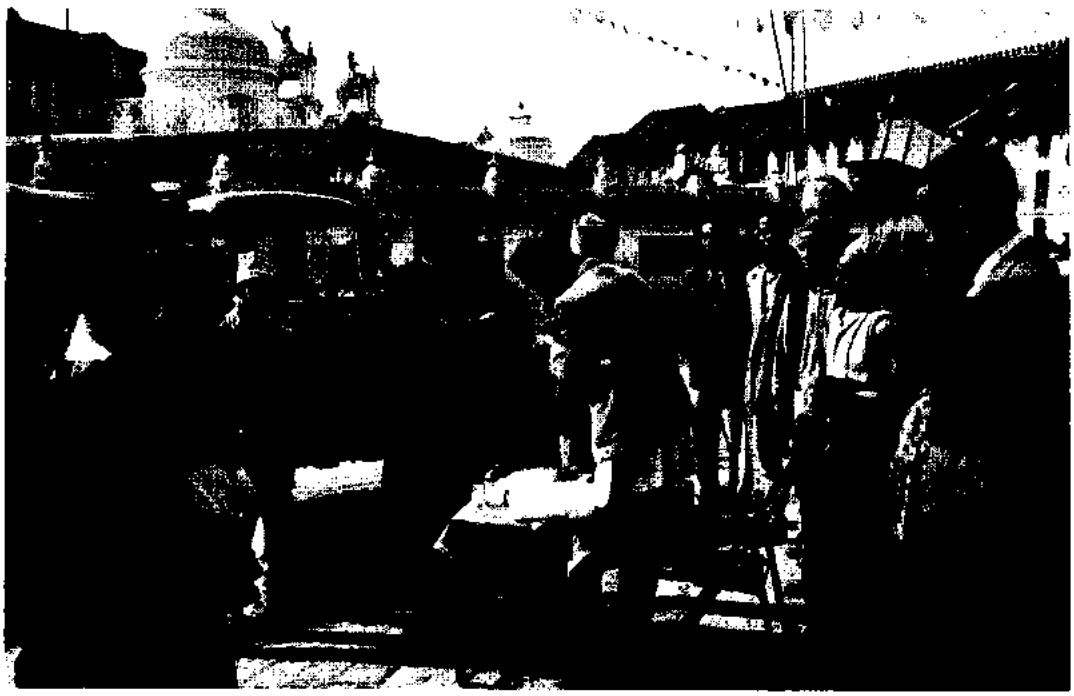


Plate 15.20. Tibetan pilgrims being vaccinated in front of a Buddhist temple at Bodnath in the Kathmandu valley, Nepal.

January 1975, when 21 cases, primarily among beggars, occurred in a large market area, and from there smallpox spread to 6 nearby villages. More vigorous containment efforts were required; thus, in January, watchguards were posted at each infected house, as was done in India. In addition, systematic search and vaccination programmes were conducted over wide areas encircling the site of an outbreak. The system had been in use in many states of India for more than a year but in Nepal, in which the population was sparse, the containment of outbreaks had been less of a problem and, with fewer personnel, it had been impossible up to this time to adopt the Indian methods of containment. With the numbers of outbreaks diminishing both in India and in Nepal, a more elaborate scheme was possible. Resistance to vaccination was usually overcome with verbal persuasion although, on occasion, police accompanied the vaccinators to lend their authority. The number of outbreaks declined rapidly, and on 6 April 1975 the last cases occurred in Nepal.

Data regarding the age distribution of cases are available for 1286 of the 1921 cases which occurred in the period 1973 1975 (Table 15.39). Smallpox in Nepal occurred more frequently among older children and adults than in India. Less than one-third of all cases were in children under the age of 5 years and 29% were in persons over 15 years of age. The fact that more cases tended to occur in the older age groups in Nepal than in India probably reflected lower levels of vaccinial immunity throughout the population as well as a lower level of naturally acquired immunity due to the relative isolation of villages. Although villages in Afghanistan were comparable in their degree of isolation, vario-

Table 15.39. Nepal: age distribution of 1286 cases of smallpox, 1973–1975

Age group (years)	1973	1974	1975	Total	
				Number	%
0–1	16	119	4	139	11
2–4	51	214	12	277	21
5–14	87	374	38	499	39
⩾15	73	273	25	371	29
Total	227	980	79	1 286	100
Total number of cases reported	277	1 549	95	1 921	–

Plate 15.21. A Nepalese vaccinator at work. The plastic holder for bifurcated needles in the foreground was designed and first made in Pakistan; the vaccine came from the USSR.

lation had been extensively practised there and many persons were immune as a result. In Nepal, however, the procedure had been largely discarded in recent decades.

Only 40 out of 1915 patients (2.1%) for whom data are available had been vaccinated before exposure—a far lower proportion than that reported from India. Several factors could account for this. In India, in which rotary lancets had long been in use, many apparent vaccination scars resulted from sepsis rather than successful vaccination. In Nepal, few had been vaccinated with the rotary lancet. Moreover, in the vast majority of instances the vaccination had been performed after 1967 so that vaccinial immunity was likely to be at a higher level.

The case-fatality rate was 21.5% (411 deaths among 1915 patients), a figure consistent with observations elsewhere in the Asian subcontinent.

At the time that the last case occurred, a reward of 100 rupees (US$9.50) was being offered to anyone reporting a case, and later this sum was increased to 1000 rupees. After 6 April 1975, however, no reported case was

confirmed and no further cases were detected in subsequent laborious house-to-house searches.

Cost of the Programme

The total outlay on smallpox eradication by the government of Nepal and by WHO during 1962–1976 amounted to US$2 378 982, or just over US$0.15 per head of population. For the period 1972–1976, approximately 2% of the Ministry's health budget was spent on the programme. The expenditure, however, was low compared with the cost of other programmes such as that for malaria control, on which, in the year 1976–1977 alone, Nepal spent more than US$4.5 million (SME/77.1, Shrestha et al.).

SIKKIM AND BHUTAN

East of Nepal in the Himalayan mountains lay 2 small sparsely settled political entities—Bhutan and Sikkim (Fig. 15.32). Bhutan, an independent monarchy, had an estimated population (in 1967) of 987 000, which was concentrated in the central and southern parts of the country and had contact through trade and travel with the inhabitants of Assam, West Bengal and Bihar in India. Between Nepal and Bhutan was the even smaller and less populous Indian protectorate of Sikkim (population in 1967, 196 000), which in 1975 became a state of India. Both areas shared a northern border with China, but few travellers crossed it.

Sikkim and Bhutan were both at risk of smallpox imported from India, although in neither area had it seemed likely that smallpox transmission could be long sustained among the population of the scattered mountain villages. Thus, until smallpox transmission was interrupted in India and Bangladesh, little support was provided by WHO to either Sikkim or Bhutan and, in fact, information about the smallpox situation in both areas was scanty until late in the Intensified Programme. With the interruption of smallpox in India, attention was directed to these and other more remote areas of the subcontinent to ascertain something of the history of smallpox and smallpox control in recent years and to confirm that transmission was not continuing.

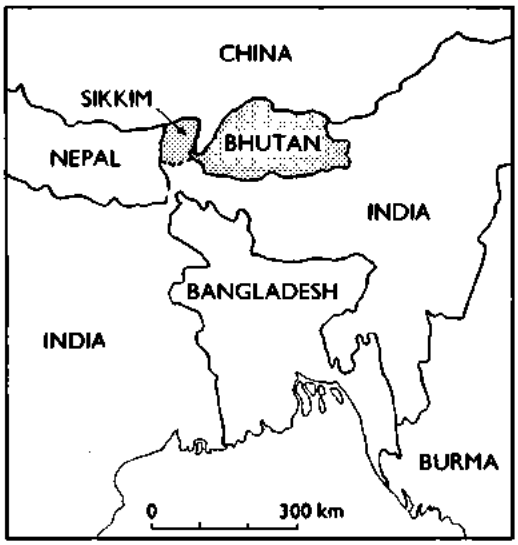


Fig. 15.32. Bhutan and Sikkim and adjacent countries.

Sikkim

Cases of smallpox had been officially reported in Sikkim since 1954. In 1966–1967, 78 cases in all were recorded at a time of high incidence in northern India. After this, no further cases were reported until 1973, when an outbreak of 34 cases occurred in Gangtok, the capital, the first case having been infected in Darjeeling, West Bengal. A second outbreak, of 11 cases, occurred that year in 2 villages along Sikkim's southern border, the source of infection again being West Bengal. No further cases were detected subsequently. Although reporting was undoubtedly very incomplete, the sporadic occurrence of smallpox was characteristic of an area in which importations were rare, and when they did occur, the disease did not spread easily.

Vaccination had been offered at the 4 district hospitals and 27 dispensaries, and the

Table 15.40. Sikkim and Bhutan: number of reported vaccinations, 1967–1975

Year	Sikkim	Bhutan
1967	114 575	35 944
1968	57 879	18 117
1969	71 812	9 029
1970	49 095	8 114
1971	36 832	43 052
1972	39 652	18 518
1973	45 801	57 375
1974	36 331	53 822
1975	28 846	25 599

number of vaccinations relative to population, at least from 1967, was quite substantial (Table 15.40). That vaccinial immunity was comparatively high was confirmed during a vaccination scar survey in November 1975, which revealed that 79% of the population had scars and only 42 of 1495 persons (2.8%) had the facial pockmarks characteristic of smallpox (Basu et al., 1979).

Bhutan

Information about Bhutan is less complete than for Sikkim. Until 1961 no health department had been established in the country. In 1964, the government created 19 posts for vaccinators, and increased the number to 25 in 1966, when a mass vaccination campaign was begun following an outbreak of 74 cases of smallpox in 1965–1966 in the capital city of Thimbu. The outbreak had begun among Indian and Nepalese workers employed in a road-building project and then spread to the local population. The number of vaccinations reported to have been performed between 1967 and 1975, however, was small in relation to the population of 987 000 (1967 estimate).

After the 1965–1966 outbreak, only 4 further outbreaks were reported. In 1967, 2 outbreaks originating in Assam caused 14 cases. The third outbreak, of 6 cases, occurred in April 1973 in a village near the south-western border with India, the initial case having been infected on a tea estate in West Bengal. The fourth outbreak, near the same border area, occurred in February 1974 and consisted of 3 cases, of which the first had been infected in Assam. Surveys conducted in 1976 to detect individuals with facial pockmarks, as well as interviews with village officials, indicate that other, unreported, outbreaks had occurred although none had produced more than a few cases. This was attributed in part to the fact that the villages were scattered and isolated, and in part to the sensible traditional practice of isolating the patient and his family at the onset of illness in a place some distance away from the village. In these circumstances, the spread of smallpox was difficult.

Sample surveys conducted in Bhutan in the autumn of 1976 confirmed that vaccinial immunity among children was generally low, especially in the central and northern parts of the country (Table 15.41).

Facial pockmarks indicative of past smallpox were not seen in anyone under 15 years of age in central and northern Bhutan but were observed in 11 children in southern Bhutan. In northern Bhutan, where adults also were examined, only 10 out of 244 persons (4%) over 15 years of age had the facial scars characteristic of smallpox, the youngest being in his late twenties.

In addition to the 11 children with facial pockmarks detected in the village surveys of southern Bhutan, 3 others were discovered during surveys of schools in this area. Nine of the 14 had experienced illness in 1967 or later, and in each instance efforts were made to identify the source of infection; all were traced to India. One had contracted smallpox while living in Allahabad, Uttar Pradesh, before moving to Bhutan. The other 8 became ill in outbreaks resulting from importations (Table 15.42).

Summary

The surveys confirmed the belief that the continuing transmission of smallpox in these sparsely populated, isolated countries had not occurred recently—even in Bhutan, in which vaccinial immunity was low. The tradition of isolating the patient and his family, observed in Bhutan, undoubtedly contributed significantly to stopping transmission. This custom, interestingly, was current throughout most mountainous areas of Asia, but was much less frequently practised in the lowlands.

Table 15.41. Bhutan: survey of vaccinial immunity and facial pockmarks in children, by age group, 1976

Area	Number of towns and villages surveyed	Number of children examined	Percentage vaccinated in age group (years)				Number with facial pockmarks
			<1	1–4	5–14	Total	
Northern Bhutan	37	152	11	30	56	44	0
Central Bhutan	12	7 952	26	55	70	59	0
Southern Bhutan	205	8 595	10	66	84	69	11

Table 15.42. Bhutan: number of reported cases of smallpox and sources of outbreaks, 1966–1974

Year of illness	Number of cases	Source of outbreak
1974 (February)	3	Assam
1973	6	West Bengal
1967	14	Assam
1966	64	West Bengal

CONCLUSIONS

From 1961, when India first decided to embark on a national eradication programme, to 1975, when the last case was detected, the programme gradually improved—in the quality of vaccine employed, in the vaccination technique used, in the reporting system, in the extent and intensity of surveillance and containment and, most important, in the quality of supervision. To undertake a national programme in a country so vast, with a population so large and a bureaucracy so complex, was inevitably difficult. To modify and redirect such a programme proved no less difficult. The dimensions of the effort, which involved at least the part-time participation of more than 150 000 field staff and contact with more than 550 million persons, are hard to grasp or communicate.

India's population, in 1967, constituted almost half of the total number of inhabitants of the endemic countries and, indeed, 15% of the world's entire population. The central direction of the enormous national campaign then in progress rested with only 1 medical officer and a small staff of clerks. In the states, of which 7 each had a population of more than 40 million, direction was generally entrusted to a single medical officer, for whom, in most instances, smallpox eradication was but a part-time responsibility. Working in the cities, towns and villages, however, were tens of thousands of vaccinators, basic health workers, family planning and malaria eradication programme staff and many other categories of health worker. Many were responsible, experienced individuals, conscientious about their jobs and willing to work, but they were seldom provided with much in the way of support or stimulus or the necessary supplies to carry out their assigned tasks. New directions or new policies were more often than not impersonally communicated by official memoranda which frequently demanded the impossible for example: "All persons in the state will be vaccinated cent per cent [100%] during the next 12 months." Vehicles stood idle and refrigerators remained inoperative for want of petrol or a few spare parts because the monetary resources provided had proved inadequate and/or fiscal procedures were so cumbersome as to prevent the disbursement of the funds. Vaccine deliveries were erratic and numerous batches were unfit for use because of the lack of refrigerated storage.

In the opinion of many, the solution to the disappointing level of productivity throughout the health sector was to eliminate special programmes such as that for smallpox eradication and to integrate all programmes into a unified primary health care programme in which each health worker would assume a multiplicity of responsibilities as a "basic health worker". This was the panacea which had been repeatedly proposed by both Indian and WHO expert groups since the 1950s. It was the course of action recommended in 1966 as India's intensive national vaccination campaign drew to a close, with smallpox almost as widespread as it was before the campaign had begun. In a number of states such integrated programmes were started in the mid- and late 1960s but the productivity of the workers was, if anything, even lower than it had been before.

Given the difficult problems and the paucity of senior leaders, the achievements of the smallpox eradication programme between 1967 and 1973 were remarkable. By the summer of 1973, smallpox transmission had been virtually interrupted in the southern states and was declining in the western states. It seemed that a comparatively modest investment in time by senior epidemiologists to help to develop surveillance and containment activities in the other states should rapidly succeed in interrupting transmission throughout India. The deplorable condition of the health services in some of these states, especially Bihar, Assam and Uttar Pradesh, was not then comprehended, nor were the coming disastrous epidemics anticipated. However, the administrative changes which were made in the summer of 1973 had profound consequences in that they permitted the vast resources of health man power in India to be utilized effectively and gave scope to the imagination and problem-solving abilities both of senior staff and of field workers. With the active support of the Minister of Health and Family Planning and

an adequate complement of senior Indian and WHO staff to travel to the field to explore alternative solutions to problems, to instruct, to assess and to measure results, field staff took an increasing interest in the programme. Knowing what should be done, they themselves sought new solutions. The onerous fiscal constraints were ultimately resolved through the use of the flexible imprest accounts provided by WHO. With the most senior Indian staff, initially Dr Diesh and later Dr Sharma, not only travelling to state capitals but also visiting field staff in districts and villages, the example was set for otherwise desk-bound lower-level supervisory staff to do likewise. By doing so, they motivated and inspired staff at all levels.

The strategy adopted for the programme also played an important role, the country being divided into 3 different areas, with the objective of preventing smallpox from re-establishing itself in smallpox-free states, of eliminating the few remaining foci in states with a low incidence, and of conducting a major offensive in the 4 states with the highest endemicity. Each of the states thus had specific goals and programmes appropriate to those goals. Measurable indices of progress in achieving eradication were important. These were identified first in terms of the numbers of cases of smallpox occurring each week and then in terms of the numbers of outbreaks in which a case had occurred during the preceding 4 weeks. In the last year of the programme, other standards were formulated to measure the quality of surveillance, of containment and of outbreak investigation. With specified and achievable objectives, all personnel could assess progress in their own area, be it a primary health care centre, a district or a state. Monthly meetings and regular surveillance reports served as refresher training, permitting new approaches to be introduced and serving as a stimulus to all concerned.

The problems that emerged after the intensive campaign was launched in the summer of 1973 were far greater than anyone had expected, but the conviction of the senior leadership and the programme's momentum were sustained in the face of often hostile criticism by some senior Indian and WHO officials, natural calamities of flood and famine, civil disorder and strikes, and the inevitable bureaucratic inertia. The programme improved so rapidly that the transmission of smallpox was interrupted in India less than 20 months after the first search had begun. Because of the quality of the programme and the confidence achieved through assessment of its merits, it was possible only 3 months after the occurrence of the last case to celebrate India's freedom from smallpox on India's Independence Day in August 1975. In no other country up to that time had it been possible to feel so confident so soon. However, over the next 2 years, the programme staff conducted the most elaborate and extensive search programme of any in Asia to confirm for themselves and—just as important—to convince an incredulous world community that India was truly free of smallpox.

What many failed to appreciate was that the achievement was not the product of a special army dedicated to smallpox eradication, but one in which existing health staff of all types participated actively in managing and executing a programme with measurable objectives. When eradication was certified in 1977, only a handful of long-term smallpox vaccinators and a few senior staff remained to be reassigned to other programmes.

As had been expected, smallpox in Nepal, Bhutan and Sikkim reflected the experience in the neighbouring densely populated Indian states. In Bhutan and Sikkim, the only special activities undertaken, aside from routine vaccination programmes, were those concerned with certifying the absence of smallpox. In Nepal, far more populous and epidemiologically more closely related to India, a special programme was required.

The programme of vaccination and later of surveillance and containment in Nepal represented its first national health programme, and one which extended to all parts of this mountainous rugged country. Since travel throughout much of Nepal was of necessity by footpath, and health facilities were non-existent in many parts of the country, district smallpox supervisors played a vital role. With encouragement from national staff and repeated refresher training, most of these local workers responded well to their responsibilities. The first national disease reporting system was established, and vaccination—all but unknown in most of the country in 1967—reached more than 90% of the population within a period of little more than 5 years. It was an impressive achievement, especially in view of the fact that the ratio of programme staff to population was at

best 1 to 20 000. Nepal's successes were different from India's but no less remarkable.

The programme in India was slow to gain momentum and undoubtedly eradication might have been attained far sooner if an adequate complement of well-motivated senior supervisors had been provided at an earlier stage. In all probability, the greatest catastrophe of the Intensified Programme would have been averted—namely, the 1971 epidemic in the Calcutta Salt Lake Refugee Camp, which led to the reintroduction of smallpox into Bangladesh and to tens of thousands of deaths.

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CHAPTER 16

BANGLADESH

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INTRODUCTION

The last case of smallpox in Asia and the last case of variola major, the more severe form of the disease, occurred in Bangladesh (Fig. 16.1) on 16 October 1975. It might not seem surprising that Bangladesh was the last Asian country to eliminate smallpox. Of all the countries of the world, it was one of the poorest and most densely populated. However, Bangladesh (East Pakistan until December 1971) had already succeeded once in interrupting transmission 5 years earlier, in August 1970. The achievement had been remarkable and unexpected, occurring just 8 months after limited resources had been diverted from an extensive mass vaccination campaign to a simple surveillance and containment programme. Most observers believed that other undetected foci would become apparent during the subsequent dry season, from October 1970 to the end of March 1971, when more rapid transmission occurred. However, 6 months went by without further cases being found. Suddenly, in March 1971, a tragic and violent civil war broke out, 10 million refugees fled to India, and health programmes and organized surveillance activities virtually ceased. However, up to the end of December 1971, no smallpox patients were admitted to the infectious disease hospitals, no cases were reported by health staff and none were detected among the continuing flood of refugees entering India.

Many of the refugees who fled to India were housed in special camps, hurriedly set up in areas near the border. They were supposed to have been vaccinated on arrival, but in several camps, including the largest, near

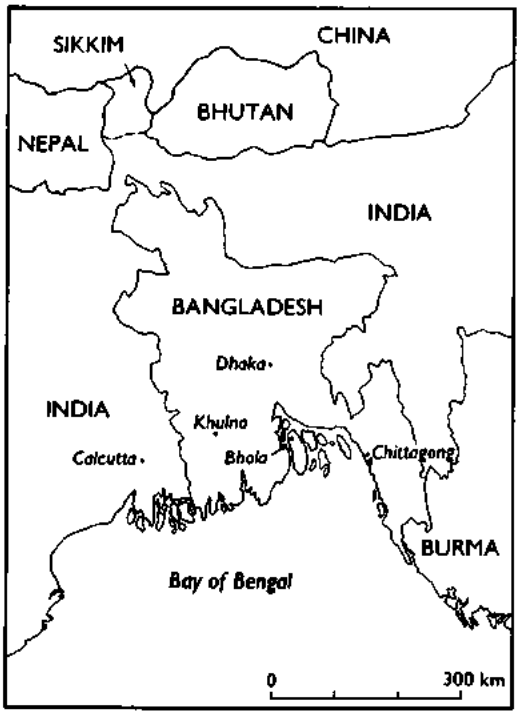

Fig. 16.1. Bangladesh and surrounding countries.

Calcutta, few were, in fact, vaccinated. Smallpox broke out in November 1971 and spread rapidly. Because cases were incorrectly diagnosed, nothing was done to contain the epidemic until late in January 1972.

Meanwhile, on 16 December 1971, Bangladesh became an independent state, and every day thereafter thousands of refugees, many of whom were infected with smallpox, began to return home. This mass migration took place at the beginning of the season of highest transmission. The health service, devastated by civil war, could not cope with the situation; epidemic smallpox swept through temporary refugee camps, cities and rural areas.

The eradication programme was reconstituted and strengthened, but, despite far more intensive efforts than had been made in 1970, transmission persisted year after year between 1971 and 1975, as one disaster followed another. At different times, famines, floods, civil disorder and the forcible displacement of urban slum dwellers caused hundreds of thousands of people to flee their homes. The national health services were reorganized at a critical time, in 1973, seriously hampering field activities; and national leaders periodically redirected the smallpox eradication programme towards mass vaccination campaigns.

In the spring of 1975, a greatly strengthened although frustrated and demoralized staff made one more concerted effort to stop transmission and ultimately succeeded in October 1975, when the last case occurred.

During its final year the eradication programme in Bangladesh utilized and further developed methods that had been elaborated over the preceding 8 years of the Intensified Smallpox Eradication Programme and employed experienced personnel from many other countries. The national programme is thus of special interest. However, if the refugees in the camps in 1971—amounting to perhaps 300 000 persons—had been vaccinated, this chapter would have been very brief; 223 000 fewer cases of smallpox would have occurred and more than 40 000 deaths would have been averted.

Of the national smallpox eradication programmes, that in Bangladesh is one of the better documented; much of the material for this chapter is drawn from a book by Joarder et al. (1980), *The Eradication of Smallpox from Bangladesh*. The book also describes the eradi-

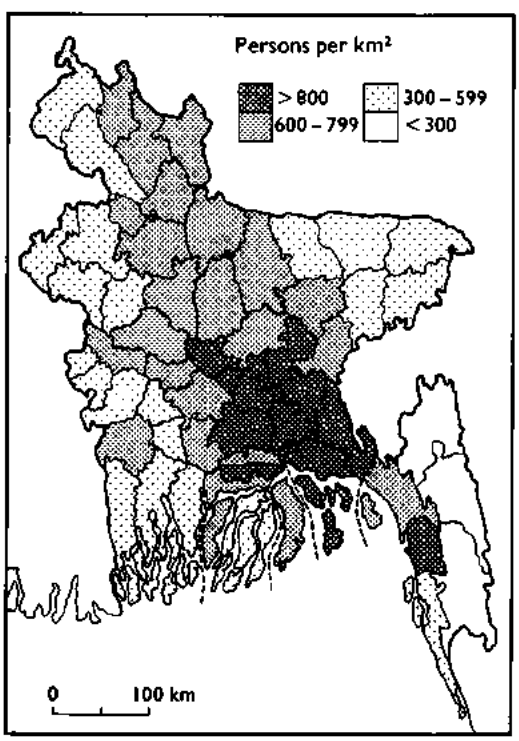

Fig. 16.2. Bangladesh: population density by subdivision in 1967.

Table 16.1. Bangladesh: administrative units in 1972

Administrative unit[a]	Number	Average number in next larger unit	Average area (km^2)	Average population
Division	4	–	36 000	17 618 000
District	19	5	7 500	3 709 000
Subdivision	57	3	2 500	1 236 000
Thana	424	7	330	166 000
Union	4 266	11	30	17 000
Village	64 493	15	2.5	1 000

[a] In 1983–1984, the structure was changed so that each Subdivision was designated a District and *thanas* were renamed *upazilas*.

cation staff's experience in the practical application of techniques for surveillance and assessment in other health programmes.

BACKGROUND

The richly fertile country of Bangladesh lies at the delta of three of Asia's great rivers—the Ganges, the Brahmaputra and the Meghna. More than nine-tenths of the country is less than 15 metres above sea level, and as much as one-third of the agricultural land is flooded during the June–September monsoon. In 1967, Bangladesh had a population of some 62 million, one of the fastest growing and with the highest density of any major country (428 persons per square kilometre). The central and southern parts of the country were the most densely settled (Fig. 16.2). Even in areas in which vaccinial immunity was comparatively high, the number of susceptible individuals per square kilometre was greater than in most endemic countries.

There was considerable population movement throughout the country. Nearly 95% of the people lived in rural areas, but 30% were landless and even those with some land of their own often sought part-time work elsewhere as tenant farmers or labourers. At planting and harvest times, hundreds of thousands of people travelled up to 200 kilometres in search of work. Although there were only 3 cities in 1974 with populations of more than 300 000—Dhaka (1.8 million), Chittagong (970 000) and Khulna (480 000)—all cities and towns had large unenumerated transient populations entering and leaving each day. A study in Dhaka in 1976, for example, showed that more than 110 000 persons passed daily through its main

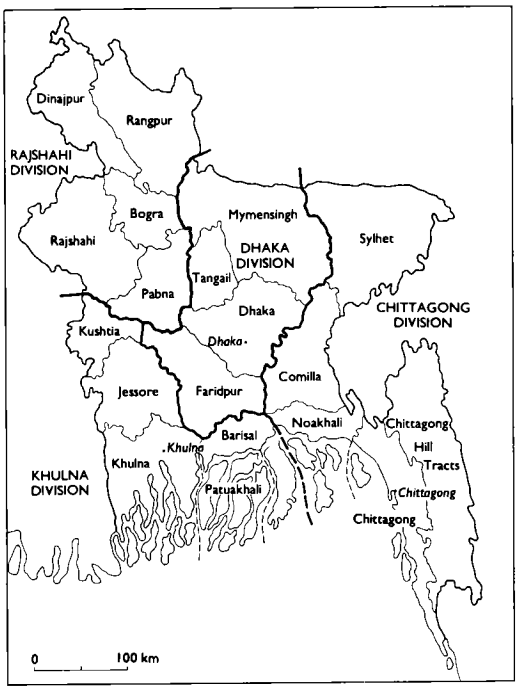

Fig. 16.3. Bangladesh: divisions and districts as of 1972.

points of entry. However extensive the movement of people, village and family ties remained especially important in this traditional Muslim society, so that those who fell ill frequently travelled long distances to be cared for in their home villages by their families. In this setting, the transmission of smallpox from urban to rural areas was rapid and widespread.

Undernutrition and malnutrition were common even when harvests were good. In 1962–1964, it was estimated that the residents of only 54% of rural households were adequately fed, and by 1975–1976 this proportion had decreased to 41%. Because of the precarious nutritional situation, even a small decrease in food supplies had a disproportionately heavy impact, causing hundreds of thousands of people to migrate from one area to another, many to the cities. At such times, smallpox spread with facility.

Travel by land was time-consuming and difficult, making it hard to supervise the programme effectively and to transport supplies to smallpox eradication staff in the field. A network of 4000 kilometres of all-weather roads radiated from Dhaka to district towns but major ferry crossings were encountered frequently and roads were often damaged or

Plate 16.1. River-boats provided transportation for many travellers in Bangladesh and, with the large crowds, smallpox spread rapidly and widely across the country.

washed out by monsoon rains. Hundreds of thousands of river-boats provided transport for many travellers; although they were slow, they were inexpensive and permitted extensive population movement, especially during the monsoon season.

The various administrative units, to which reference is made later, as well as their average area and population size, are enumerated in Table 16.1. Division and district boundaries are shown in Fig. 16.3.

Each village was composed of a number of *baris*. A *bari* usually corresponded to a household, but it also referred to a compound occupied by an extended family and sometimes included the houses of servants and other employees in the wealthier families.

In each district and subdivision, civil surgeons were responsible for all curative and preventive services except for the malaria eradication programme, which operated as an autonomous activity until late 1973. One or two medical officers were usually assigned to each *thana*, the basic administrative unit, but preventive measures were the responsibility of a sanitary inspector, who supervised some 5–10 government health assistants. Each government health assistant—a category of staff usually recruited locally—was in charge of a union. Many of the government health assistants had had no more than an elementary-school education; none were well paid or adequately supervised. Until late 1973, the malaria eradication programme, one of the best of its kind in Asia, had an independent but roughly parallel structure. Its staff, however, was of a generally better quality, received higher pay and was far more reliably supervised.

SMALLPOX AND ITS CONTROL BEFORE 1968

As elsewhere in the Indian subcontinent, only the variola major variety of smallpox was known to have occurred, and this fertile, heavily populated delta area may well have been one of the earliest endemic areas in Asia. Until late in the 19th century, protection was afforded primarily by variolation, performed by indigenous practitioners. Vaccination, with liquid vaccine produced in Calcutta, was introduced in 1860 in areas near Calcutta and in certain of the district towns of what is now Bangladesh. In 1874, the authorities decided that variolation should be abolished and they encouraged the variolators to replace variola

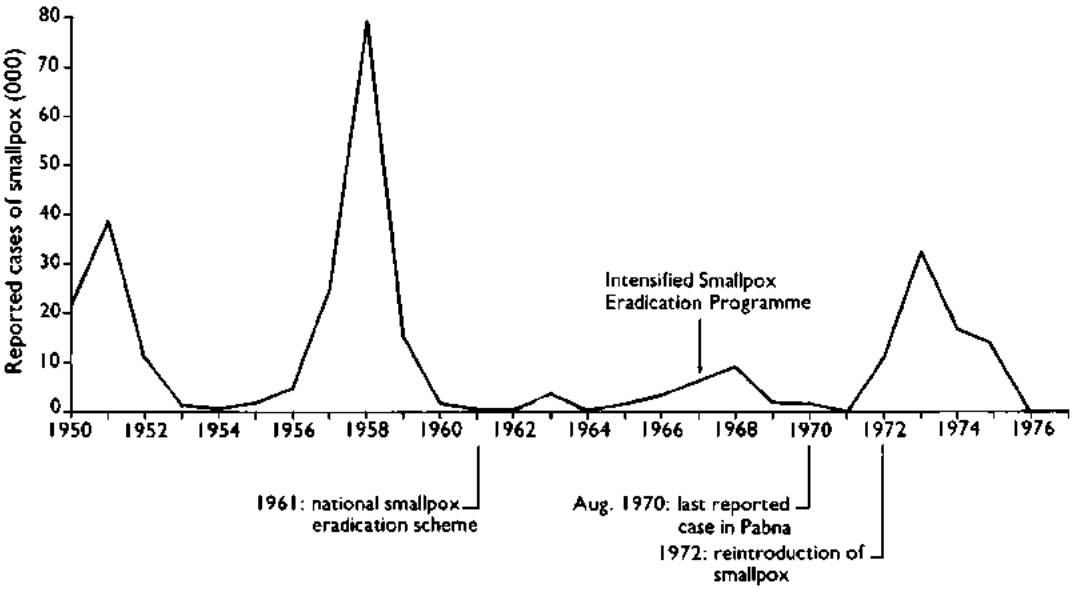

Fig. 16.4. Bangladesh: number of reported cases of smallpox, by year, 1950–1977.

virus by vaccinia virus. By the turn of the century, as vaccination became more widely available, variolation ceased altogether. In 1947, the production of liquid vaccine began in Dhaka, and up to 1961, vaccination was performed throughout the country by government-paid vaccinators supervised by health inspectors in each *thana*. The extent of vaccinial immunity is unknown but with only the thermolabile vaccine available in this subtropical area, many vaccinations were probably unsuccessful.

Smallpox was known in Bangladesh as *boshonto*, the Bengali word for spring, the season of highest incidence of the disease. As in India, major epidemics were recorded every 4–7 years. After 1947, the year in which Pakistan became independent, major epidemics were recorded in 1951 and 1958 (Fig. 16.4), the latter being so extensive that assistance for its control was sought from other countries. In all, 79 060 cases with 58 891 deaths were reported that year, a figure which, because of poor reporting, was undoubtedly one-tenth or less of the actual total. One of the groups providing assistance was a team from the United States Communicable Disease Center (later, the Centers for Disease Control), Atlanta. This team estimated that 60–70% of the people had vaccination scars but could find no correlation between the level of vaccinial immunity and the intensity of the epidemic in different areas. The team members were impressed by the size of the epidemic and the density of the population and suggested that "the number per square mile of unvaccinated persons would be a better index of the susceptibility ... than the index that is ordinarily used, the proportion of the population that has been vaccinated" (Usher, 1960). They concluded that the "feasibility [of global eradication] under presently existing circumstances is dependent on the likelihood of success in countries where eradication is likely to be most difficult to accomplish and the obstacles greatest. One of these countries is Pakistan ..." (Usher, 1960). As an outcome of the epidemic, it was decided to develop a laboratory in Dhaka capable of producing freeze-dried vaccine, but substantial quantities of such vaccine did not become available until 1966.

Resolution WHA12.54, adopted by the Twelfth World Health Assembly in 1959, called on all countries to join in a mass vaccination programme with the aim of eradicating smallpox. This initiative was enthusiastically supported by the Pakistani government and a campaign commenced in East Pakistan in 1961. The intention was to vaccinate the entire population within two or three years.

During the 3-year period 1961–1963, 72 million vaccinations were reported to have been performed and, during the succeeding 3

years, 68 million more—in all, more than twice the population of the country (Table 16.2). From field observations in 1967 and 1968, it was apparent that the reported number of vaccinations was greater than the number actually performed and, as was the case elsewhere in Pakistan and in India, the most accessible persons, such as schoolchildren, were vaccinated repeatedly while others were not vaccinated at all. Nevertheless, vaccinial immunity in the population undoubtedly reached higher levels than ever before. Only 69 cases of smallpox were reported in 1964, and 316 in 1965. In 1966, the number of cases again increased, reaching 3207 that year and 6648 in 1967.

During the summer of 1967, epidemiologists who had conducted studies of smallpox in West Pakistan (see Chapter 14) decided to undertake similar studies in rural East Pakistan. A combined team from the Pakistan Medical Research Centre in Lahore, the Cholera Research Laboratory in Dhaka, and WHO studied the epidemiology of smallpox in an area in which cholera vaccine trials were then in progress. These investigations, along with those in West Pakistan, were the most comprehensive epidemiological studies conducted during the entire global eradication programme and provide an interesting overview of the smallpox situation at that time in one subdivision of the country (Thomas et al., 1971a,b).

The area studied was Matlab *Thana*, Comilla District, 65 kilometres from Dhaka; it included 132 small rural villages (population, 113 000) scattered over approximately 200 square kilometres. Vaccinators had been employed in the district since 1930, travelling from village to village to vaccinate newborn children and revaccinate others, using the rotary lancet and liquid vaccine. Comilla District had served as a pilot programme area for the 1961–1963 mass vaccination campaign and, for this operation, additional vaccinators had been employed. Therefore, as the investigators noted, vaccinial immunity among individuals over 5 years of age may have been better than in other parts of East Pakistan.

In May 1967, experienced interviewers, employed in the cholera vaccine trials, visited each house throughout the area to assess vaccinial immunity; in all, 103 539 persons were examined. In July, each house was again visited in an effort to identify, by means of an interview, all cases which had occurred between 1 July 1966 and 30 June 1967.

Of the people examined, 80.8% had a vaccination scar, the largest proportion of the unvaccinated being among children under 5 years of age (Table 16.3). This age group should have been vaccinated during the "maintenance vaccination" campaign, but, as is apparent, that programme was far from satisfactory.

Thirty different outbreaks, occurring in 27 villages, with a total of 119 cases, were identified. Of these, only 5 outbreaks and 13

Table 16.2. Bangladesh: population and number of reported vaccinations and number of reported cases of smallpox, 1961–1976[a]

Year	Population (millions)	Primary vaccinations		Revaccinations		Number of reported cases of smallpox
		Number (thousands)	% of population	Number (thousands)	% of population	
1961	52.9	374	0.7	22 070	41.7	660
1962	54.2	3 509	6.5	24 145	44.5	610
1963	55.6	2 546	4.6	19 481	35.1	3 735
1964	56.9	1 490	2.6	18 104	31.8	69
1965	58.4	1 505	2.6	18 245	31.3	316
1966	59.9	2 041	3.4	26 275	43.8	3 207
1967	61.6	2 266	3.7	26 475	43.0	6 648
1968	63.2	2 626	4.2	30 201	47.8	9 039
1969	64.9	1 974	3.0	29 636	45.6	1 925
1970	66.7	1 602	2.4	16 991	25.5	1 473
1971	68.5	432	0.6	5 835	8.5	0
1972	70.5	2 496	3.5	34 215	48.6	10 754
1973	72.5	3 660	5.1	33 237	45.9	32 711
1974	74.5	4 445	6.0	10 669	14.3	16 485
1975	76.6	5 773	7.5	17 905	23.4	13 798
1976	78.7	848	1.1	4 355	5.5	0

[a] Population estimates from United Nations (1985).

cases had been officially reported but, as in West Pakistan, the reported outbreaks included 5 of the 6 largest, in which 54 cases had occurred. In 7 outbreaks, special vaccination control campaigns had been conducted by government vaccinators but with little apparent effect.

The age distribution and case-fatality rates (Table 16.4) were similar to those observed elsewhere in Pakistan and in India. Thirty-four (29%) of the cases were in children under 5 years of age, 55 (46%) in individuals aged 5–19 years and 30 (25%) in those aged 20 years and over. Thirty-four of 111 persons (31%) of known vaccination status had previously been vaccinated, all except 6 of them being 10 years of age and older. With data available regarding the vaccination status of the population as a whole, it was possible to calculate vaccine–efficacy ratios by age based on vaccination at some time in the past (WHO/SE/69.11, Thomas et al.). The ratios showed 94–96% protection for those aged up to 14 years; 89% for those aged 15–24 years; and 74% for those aged 25 years and more. The ratios were remarkably high, although not so great as those found in South America, in which only the mild variola minor variety of smallpox was present.

The epidemiological pattern of spread was of special interest. Thirteen of the 30 outbreaks consisted of only a single case, and in 9 others the disease was not transmitted beyond the initially infected *bari*. Moreover, 24 of the outbreaks terminated after less than 2 generations of spread. Despite the density of population and a lower level of vaccinial immunity, smallpox tended to spread less rapidly and to remain more localized than in West Pakistan. The sources of 22 outbreaks were identified. All but 1 of the sources were outside the study area and 15 of the 22 originated in cities of 100 000 inhabitants or more, in which only 5% of the population of the province resided. In this study population, continuing transmission of smallpox from village to village had not occurred and, in fact, no cases whatever were detected whose onset took place between September and December 1966.

The investigators concluded that it was even more important in East than in West Pakistan to eliminate smallpox from urban areas, an objective which, if achieved, would prevent a high proportion of rural cases. Moreover, it appeared that most outbreaks in rural areas might be contained simply by vaccinating the inhabitants of the affected and neighbouring *baris* rather than the population of the entire village. Noting the high vaccine–efficacy ratios, the investigators recommended that a continuing programme of maintenance vaccination should concentrate on vaccinating those who had never been previously vaccinated, especially children aged 5–14 years not attending school and landless labourers working in urban areas—identified as the two groups most likely to transmit smallpox from place to place.

For a settled population and one which was as well vaccinated as that of Matlab *Thana*, the recommendations were sound and in 1970 the programme would substantiate their validity. However, when mass migrations of refugees took place, as happened repeatedly after the country became independent, and when smallpox outbreaks occurred in areas in which vaccinial immunity was low, more extensive containment measures were found to be required.

Table 16.3. Matlab *Thana* study area, Comilla District: vaccination scar survey, 1967, by age group[a]

Age group (years)	Number examined	With vaccination scar	
		Number	%
<1	3 356	207	6.2
1–4	15 044	6 206	41.3
5–9	19 995	16 045	80.2
10–14	14 278	13 178	92.3
≥15	50 798	48 009	94.5
Total	103 539[b]	83 695	80.8

[a] From Thomas et al. (1971a,b).
[b] Includes 68 persons of unknown age of whom 18 were without a vaccination scar.

Table 16.4. Matlab *Thana* study area, Comilla District: number of reported cases of deaths from smallpox and case-fatality rates, 1967, by age group[a]

Age group (years)	Number of cases	Number of deaths	Case-fatality rate (%)
<1	10	7	70
1–4	24	10	42
5–9	38	6	16
10–19	17	3	18
≥20	30	3	10
Total	119	29	24

[a] From Thomas et al. (1971a).

THE WHO-SUPPORTED ERADICATION PROGRAMME BEGINS, 1968

In July 1967, Dr Ehsan Shafa, the regional smallpox adviser from the WHO Regional Office for the Eastern Mediterranean, and Arita held meetings with government officials in Islamabad, the national capital, and Dhaka, the capital of East Pakistan, and developed a draft plan of operations. The government agreed to the plan in principle and submitted a letter to the WHO Regional Office requesting assistance. This letter permitted funds to be obligated and supplies to be procured well before a more formal agreement was signed by WHO and the government, inevitably a long process. (The agreement was not, in fact, signed until 26 April 1968.)

The principal component of the plan was a mass vaccination campaign, as in West Pakistan. It was thought that a well-organized campaign and concurrent assessment of the results, coupled with the use of freeze-dried vaccine and bifurcated needles, would achieve a higher level of vaccinial immunity than had previous campaigns. Provision was made for surveillance teams in areas in which mass vaccination campaigns were in progress, but the concept of a national surveillance programme did not take shape until 1969. Although the findings and recommendations of the research team were available to national and WHO staff by early 1968, they were almost wholly ignored in the implementation of the national programme.

The plan called for a special full-time staff comprising a headquarters office with physicians and supporting staff, 2 medical officers in each district, a medical officer in each subdivision and vaccination teams totalling some 1500 persons. The programme was to begin in 6 of the 17 districts and was to be completed in these districts during the first year of operation. Vaccination campaigns would subsequently be conducted in the remaining districts during the second and third years. The vaccination teams would move progressively from one union to the next and assessment teams would check the coverage. It was expected that sufficient freeze-dried vaccine could be produced by the Dhaka laboratory for both East and West Pakistan. For the first year, WHO provided the following items: 10 motor vehicles, 130 motor cycles, 5 boats and 1500 bicycles, in addition to other supplies. Up to the end of 1971, WHO support to the programme ranged between US$ 67 000 and US$ 201 000 per annum (Table 16.5). It did not increase significantly until 1974.

A WHO epidemiologist, Dr Karel Markvart, arrived in January 1968 to help with the

Plate 16.2. **A**: Mohammad Ataur Rahman (b. 1925) as deputy director of the vaccine production laboratory in Dhaka, Bangladesh, played an important role in its development and, later, as health adviser to the Planning Commission, provided essential support for national mobilization for smallpox eradication in 1975. **B**: Karel Markvart (b. 1933) was a WHO adviser to the programme in Bangladesh from 1968 to 1971.

Table 16.5. Bangladesh: support provided to the smallpox eradication programme, 1967–1977, by source (US$)[a]

Year	Government[b]	WHO regular budget	WHO Voluntary Fund for Health Promotion[c]	United Nations Relief Operation/UNICEF	Total
1967	..[d]	(201 080)	–	–	201 080
1968	..[d]	(73 847)	–	–	73 847
1969	..[d]	(113 797)	–	–	113 797
1970	..[d]	(129 363)	–	–	129 363
1971	..[d]	(67 216)	–	–	67 216
1972	562 500	106 041	12 431	435 000	1 115 972
1973	1 625 000	207 862	76 529	–	1 909 391
1974	2 137 000	227 654	199 757	–	2 564 411
1975	1 582 000	126 049	3 074 788	–	4 782 837
1976	1 000 000	119 280	1 719 425	–	2 838 705
1977	1 000 000	128 300	998 530	–	2 126 830

NOTE: WHO records for 1967–1971 reflect support to both East and West Pakistan. Approximately half (the figures shown in parentheses in this table) was provided to East Pakistan. The principal contributors to the WHO Voluntary Fund for Health Promotion were Canada, Denmark, Norway, Sweden and the United Kingdom. The United Nations Relief Operation, Dacca (UNROD), provided US$415 000; UNICEF provided US$20 000.

[a] From Joarder et al. (1980) and WHO financial records.

[b] Estimated.

[c] Not including the cost of 45.3 million doses of vaccine.

[d] .. = data not recorded.

organization of the national mass vaccination campaign. The problems in mobilizing and training so large a staff were staggering. Additional government funds were required to implement the programme (2.5 million rupees—i.e., US$ 250 000) but because the agreement was not signed by the government until April 1968 no funds were made available before the fiscal year beginning 1 April 1969. A full-time national counterpart—Dr A. M. Mustaqul Huq, an able and dedicated public health officer—was not assigned until July 1969.

In 1968, the organization of health services in 12 of the 19 districts was chaotic. In the 12 so-called "non-provincialized" districts, there was a dual management structure. A district council appointed and paid the salary of a district health officer, who was responsible for preventive activities, while the provincial government appointed and paid a civil surgeon, who was responsible for both curative and preventive activities. At the next lower level, the subdivision, health activities were under the direction of a subdivisional medical officer of health, appointed and paid by the provincial government. He was required to supervise sanitary inspectors, who were appointed and paid by district councils. In their turn, they were expected to supervise vaccinators, who were recruited and paid by the provincial government. In addition, municipal staffs were independently directed by municipal committees and were not responsible to provincial or subdivisional government health staff. Appointments by district councils and municipal committees were as often decided by political considerations as by qualifications; discipline in performance and coordination were chronic problems which plagued the programme throughout its course. In the remaining 7 districts, the health services had been "provincialized" and there, with all health staff appointed and paid by the provincial government, the health structure operated more effectively.

At the end of 1968, the Dhaka municipal committee was persuaded to provide funds and staff to undertake a mass vaccination campaign, in part as a pilot study, but also in recognition of the role of this urban area as the country's principal focus of the spread of smallpox. The campaign was reasonably successful as measured by a vaccination scar survey; by the end of the campaign, more than 90% of the population had vaccination scars (Table 16.6). After May 1969, no smallpox cases were detected in Dhaka for more than 2 years.

Table 16.6. Dhaka Municipality: vaccination scar survey, 1969, by age group

Age group (years)	Number examined	% with vaccination scar
0–4	1 387	76.8
5–14	1 951	93.2
⩾15	1 695	98.0
Total	5 033	90.4

Table 16.7. Bangladesh: vaccine production at the Dhaka laboratory and vaccine donations, 1972–1977

Year	Number of vials	
	Produced by the Dhaka laboratory	Donated by other countries
1972	343 380	26 000
1973	807 000	190 000
1974	963 500	453 000
1975	730 152	1 136 000
1976	458 750	0
1977	703 600	0

Vaccine production, meanwhile, proved to be an unexpected problem. The quantity of vaccine produced was less than had been expected and barely sufficient to supply East Pakistan. Between 1966 and 1971, the laboratory produced an estimated total of 4 million vials of freeze-dried vaccine. Vaccine quality was said by the laboratory director to be satisfactory, but when samples from 7 batches were tested in the WHO smallpox vaccine reference centre in Bilthoven, Netherlands, in late 1968, only 3 met the accepted standards. Thereafter, the director permitted no one to have access to the laboratory's records. He asserted that the vaccine was satisfactory, but examination of a further 10 batches in 1969 showed that only 3 were up to standard. Because of production problems, a consultant was recruited by WHO to work with the laboratory staff and after this the quality of the vaccine improved and the records again became accessible. However, some difficulties in producing a stable vaccine persisted throughout the programme.

Vaccine production data by year are available only for the period 1972–1977. The quantity produced was gradually increased after the provision by WHO of additional equipment and supplies, so that by 1973 more than 10 000 vials a week were being manufactured. Nevertheless, up to 1975, additional vaccine was required and this shortfall was met by a number of donors through contributions to the WHO vaccine reserve stocks (Table 16.7).

In April 1969, the government-funded posts for the vaccination campaign were finally established, but recruitment proved to be such a cumbersome procedure that not until January 1970 did sufficient staff become available to permit mass campaigns to begin in 15 of the 21 subdivisions in 7 of the country's 19 districts. In the execution of the programme and in the reporting of cases, it was agreed that the divisional and district health authorities would be bypassed, thus streamlining the structure so that only 4 levels would be involved in administrative direction and case reporting—headquarters, subdivisions, *thanas* and unions.

The vaccination campaign made slow progress, however. By November 1970, the teams had vaccinated only 4.5 million persons, little more than 6% of the population of the country (Sommer et al., 1973). Meanwhile, local vaccinators reported that they had vaccinated 32.8 million people in 1968 and 31.6 million in 1969, although these figures were considered to be inflated. In 1970, vaccination scar surveys in the 7 districts in which mass vaccination had been performed showed 4 in which the proportion of the population with vaccination scars ranged from 64.9% to 72.1%, substantially lower than the 80.9% found by the research team in Comilla. In the other 3 districts, the proportions with vaccination scars were, respectively, 75.6%, 77.5% and 86.2%.

The number of reported cases reached a peak of 9039 in 1968, the highest total in a decade, but declined to 1925 in 1969. What, if anything, this implied was unknown since little had been done to improve the reporting system.

INITIATION OF SURVEILLANCE–CONTAINMENT AND THE INTERRUPTION OF TRANSMISSION, 1970–1971

It had been agreed that in addition to the vaccination staff, there should be a surveillance team for each subdivision in which the mass vaccination campaign was conducted. As the plan of operations stated, the team would (1) control any reported attack of smallpox, and (2) if no cases were reported, vaccinate any person who had been missed after the operational (vaccinator) group had left the area. This first official recognition that there should be surveillance teams was encouraging but, conceptually, still far removed from the objective of establishing teams solely responsible for developing the reporting system, detecting cases and containing outbreaks throughout the country.

In November 1969, a WHO intercountry seminar on smallpox was convened in Dhaka which illustrated, on the basis of reports from western Africa and Brazil, what could be

achieved with more effective case detection and outbreak containment. East Pakistan had reported only 4 cases in September and 1 case in October 1969. With so few reported cases, it was decided that from January 1970 an effort would be made to investigate every reported case. A surveillance section, headed by a medical officer, was established and 1 central and 4 divisional surveillance teams were recruited to improve reporting and to investigate outbreaks throughout the country. Because government travel allowances were too meagre to cover even the most modest board and lodging, WHO agreed to provide the teams and other senior supervisors with a supplementary per diem allowance to permit them to travel in the field. The leaders of the 4 divisional teams, Dr M. A. Sabour, Dr M. Yusuf, Dr M. Shahabuddin and Dr M. A. Khan, proved to be exceptionally able and dedicated and served in this capacity throughout the entire programme. In January 1970, the first monthly surveillance report was issued, and this series continued to appear, with interruptions due to civil war, throughout the programme.

Because the time of Dr Markvart and Dr Huq was fully taken with the complex logistics of the mass campaign, Arita was assigned from WHO Headquarters for the months of February and March to help to develop the surveillance programme. In collaboration with the newly constituted surveillance teams, he investigated reported outbreaks in various parts of the country. To the surprise of all concerned, the teams discovered that cases being reported from the central and southern parts of the country were not smallpox but chickenpox and other skin diseases. On the other hand, in a northern district, the investigation of a newspaper report of 6 cases led to the detection of 93 cases of smallpox. By the end of March, it appeared that smallpox was localized in only 5 northern districts of the country. Arita suggested that the vaccination campaign should be temporarily suspended in favour of an emergency surveillance–containment campaign whose objective would be to interrupt transmission before the monsoon rains. With the agreement of a newly appointed and highly competent Minister of Health, Colonel M. M. Haque, and after the surveillance teams had been specially trained, such a campaign began; it was one of the most dramatically successful of the entire global eradication programme.

To facilitate surveillance, the reporting system was changed. The detection and identification of cases had depended on a traditional routine in which a local government employee, the chowkidar (who served also as the village watchman), was responsible for the weekly reporting of births, deaths and notifiable diseases to the *thana* headquarters. The chowkidars were frequently illiterate, poorly paid and ineffectual. Reports received at the *thana* were forwarded by mail to the subdivision, and then to the statistical section of the Ministry of Health. Reports were submitted sporadically, often after delays of several weeks, through a mail system that was anything but reliable.

Beginning in April 1970, all health workers and the malaria eradication programme staff were asked to report each suspected case of smallpox they encountered to the *thana* sanitary inspector. The better-paid, better-supervised and generally more responsible malaria eradication workers visited all houses throughout the country once every 2 weeks, searching for persons with fever who might have malaria and confirming this by the examination of blood smears. For them to report suspected cases of smallpox entailed little additional work and no disruption of activity. *Thana* sanitary inspectors were instructed to forward weekly reports of all cases in their *thana* to the subdivisional medical officers. They in turn were to report cases by telegram rather than by mail to the Dhaka smallpox eradication programme headquarters. When outbreaks were detected, the subdivisional medical officers as well as the *thana* health inspectors were instructed to investigate and contain them. This system brought health workers into the reporting system and streamlined reporting by introducing telegraphic notification directly from the subdivision to the smallpox eradication headquarters, thus bypassing the largely uninterested bureaucracy of the statistical section of the Ministry of Health.

The investigation of outbreaks generally confirmed the findings of the Comilla study: that most outbreaks originated in cities; that the spread of smallpox from village to village was surprisingly infrequent; and that outbreaks could be readily contained by vaccinating the inhabitants of an infected *bari* and those of a few *baris* surrounding it. In the northern part of the country, in which health services were less adequate and vaccinial

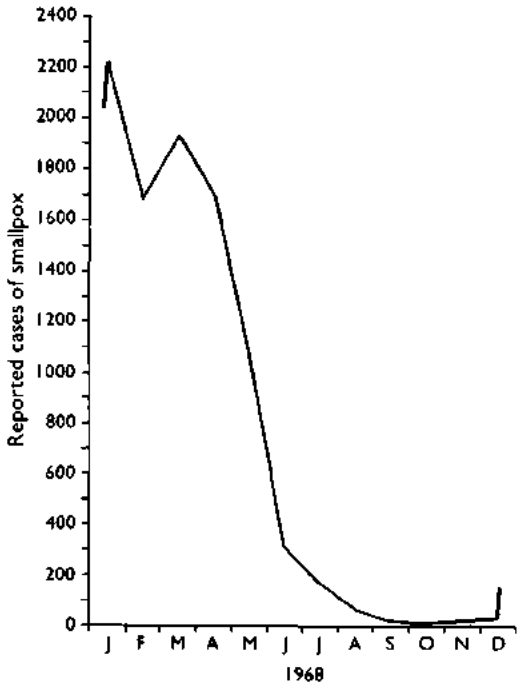

Fig. 16.5. Bangladesh: typical seasonal variation in smallpox incidence, as shown by the number of reported cases in 1968.

immunity was lower, village-to-village spread was documented in 3 *thanas* in which 13 outbreaks and 149 cases had occurred. Even here, however, the spread of smallpox was slow and although 3–7 months had elapsed between the introduction of smallpox and its detection, there were comparatively few cases in each generation of transmission and the outbreaks were readily contained (*Wkly epidem. rec.*, 1970b). Between January and March 1970, 1024 cases were detected and reported but many of these represented cases which had occurred some months previously. Few active cases were discovered.

In the entire country, only 263 cases were detected in April and only 116 in May. Moreover, the cases were localized: 4 out of 19 districts accounted for all but 59 cases. In June, the 5 surveillance teams were assigned to work intensively in the remaining infected areas and 10 surveillance teams previously working with the vaccination teams were also sent to these areas to contain outbreaks. Thirty-eight cases were discovered in June, 23 cases in July, and 9 cases in August. In August, the teams detected and contained the last known outbreak—in Pabna District. Effective surveillance continued for another 6 months but no further cases could be found.

In March 1971 civil war broke out, and until December 1971 the country was totally disrupted. During this period, it is estimated that between 1 and 3 million civilians died, 10 million refugees fled to India and an estimated 16.6 million people left their homes for other parts of the country (Chen & Rohde, 1973). Bridges were blown up, 1.5 million houses were destroyed, and severe famine occurred (Greenough & Cash, 1973).

Such evidence as is available substantiates the belief that, until 16 December 1971, when Bangladesh became independent, endemic smallpox was absent from the country—a smallpox-free interval of 16 months. During the period of civil war, no cases were found in any of the major cities, the usual sites of endemic transmission. The divisional surveillance teams were proud of their achievements and continued to travel widely throughout the country—albeit at considerable risk—seeking information about possible cases but finding none. The refugees who streamed ceaselessly across the border throughout this period were reasonably thoroughly screened by Indian civilian and military health staff in an effort to detect cases of smallpox, but none was discovered. Moreover, when smallpox was reintroduced into Bangladesh, investigation revealed that the primary source of each outbreak was a refugee who had contracted the disease in 1 of 4 infected refugee camps in India or on the way home. During April 1972, almost all cases occurred among returning refugees and their immediate contacts (Sommer et al., 1973).

The comparative ease and rapidity with which smallpox transmission was interrupted in Bangladesh in the summer of 1970 was in stark contrast to the staggering difficulties which were to mark the 4 years following its reintroduction. In retrospect, the timing of the 1970 spring surveillance–containment campaign had been ideal, from the standpoint both of the season and of the longer-term periodicity of smallpox. It had begun in the late spring, when rates of transmission customarily declined and many outbreaks terminated spontaneously (Fig. 16.5). With regard to the longer-term periodicity, smallpox incidence had peaked in 1968, with 9039 cases, and in 1969 the annual reported incidence had declined sharply to 1925 cases. In 1970, it is probable that no more than 150–200 cases would have been reported had not

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Plate 16.3. Bangladeshis, infected with smallpox while living as refugees in India, returned to their newly independent country, only recently freed of smallpox, from December 1971. Travelling in crowded trucks and trains, many lived in resettlement camps until their houses could be rebuilt. Smallpox spread widely and rapidly through the camps and across the country.

the special programme improved the completeness of notification. Even so, only 1473 cases were recorded. Moreover, at this time, neither flood, drought nor civil disorder resulted in famine and the extensive refugee movements which were to mark succeeding years. In some ways, the success of the 1970 campaign had a negative effect by engendering an unwarranted degree of optimism that such a favourable outcome could be achieved as readily and as rapidly again in Bangladesh as well as in other parts of the subcontinent.

THE REFUGEE CAMPS AND THE REINTRODUCTION OF SMALLPOX, DECEMBER 1971–MAY 1972

Of the estimated 10 million persons who left the country, most were housed in crowded camps. The largest, near Calcutta, was the Salt Lake Camp which sheltered an estimated 200 000–300 000 refugees. Government priority was given to supplying food, shelter and sanitary facilities. As noted in one report (Rohde & Gardner, 1973):

"The provision of relief to 10 million refugees ... represented a monumental humanitarian achievement. That mass starvation and galloping epidemics did not consume a greater portion of the refugee population is a tribute to the leadership, dedication and energy of the Indian Government ...

"In contrast to the efficient conduct of the overall relief effort, authority over health programs was not invested in any one group or person ... As a result, health policies and programs often lacked focus, direction, and coordination."

The provision of smallpox vaccination was one of these policies.

The Indian Ministry of Health had instructed state governments to ensure that all refugees were vaccinated against smallpox. In some camps, vaccinations were given by government staff and/or the personnel of voluntary relief agencies, and the conscientious performance of this task was confirmed by visiting Indian and WHO staff. However, state officials did not permit national health personnel or WHO staff to visit the camps in West Bengal so confirmation there was not possible. Medical care in the Salt Lake Camp was under the supervision of a voluntary relief agency; at that camp, as it was learned later, vaccination was ignored. It is likely that cases of smallpox began to occur in November, the source of infection being villages in West Bengal. The cases were recorded as chickenpox by the health staff.

BY COURTESY OF D.J.M. TARANTOLA, 1976

Plate 16.4. *Left to right*: D.J.M. Tarantola, WHO smallpox eradication adviser in Bangladesh, 1974–1977; M. Sathianathan, a medical officer in Bangladesh, who had previously served as the WHO adviser for smallpox eradication in Nepal; A.K. Joarder, Assistant Director of Health Services of Bangladesh and director of the national smallpox eradication programme, 1972–1977.

The epidemic was discovered by chance. On 19 January 1972, an American epidemiologist thought he could identify cases of smallpox in a television film of the camp transmitted to the USA. He telephoned the Communicable Disease Center, which telephoned WHO Headquarters. WHO telexed the government of India, which in turn contacted the West Bengal Ministry of Health. Although the state Director of Health Services categorically denied there were cases, one of the national staff flew to Calcutta and immediately found numerous patients. The isolation of cases and vaccination began on 23 January, but by then it was too late. On 16 December 1971, Bangladesh had become an independent country and refugees began returning home forthwith. By mid-January, an estimated 50 000 had left the Salt Lake Camp. Infectious cases, patients in the incubation period and unvaccinated contacts were all loaded together on trucks for the trip to the border. It was the season when the transmission of smallpox was most rapid and with 26 million displaced persons moving from place to place, herded together in temporary camps and crowding the bustees (city slums), smallpox spread rapidly.

Under the best of circumstances the problem would have been difficult to cope with but at this time the health services were

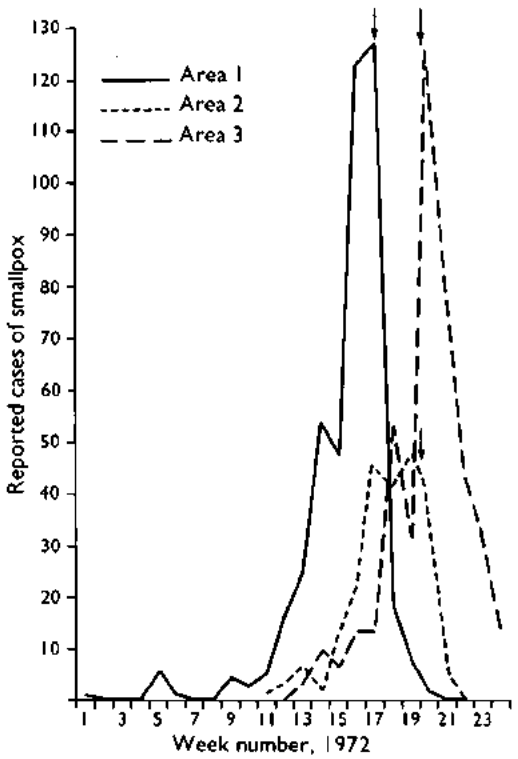


Fig. 16.6. Khulna Municipality: number of reported cases of smallpox in 1972 by week of onset in 3 areas of the city. Arrows indicate the week surveillance–containment activities started in each area.

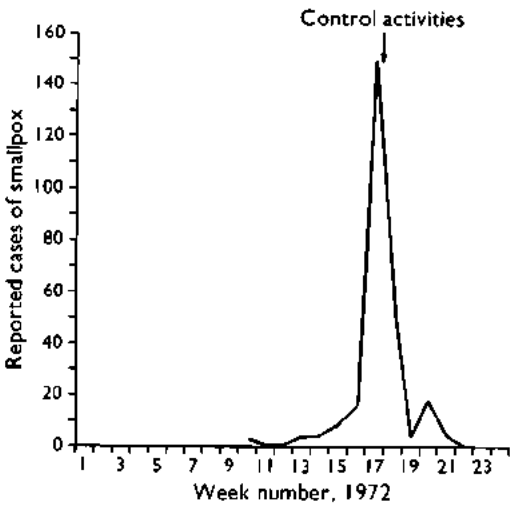


Fig. 16.7. Kalishpur Bihari camp: number of reported cases of smallpox in 1972 by week of onset.

seriously disrupted. So many motor vehicles had been damaged or stolen that less than half remained in working order, and only one-third of the number of bicycles required were available. Boats had been damaged or sunk and because of the destruction of roads, bridges and ferries, travel from place to place was difficult and time-consuming.

Arita, then on duty travel in India, flew immediately to Dhaka, and working with Dr M. Huq, the Director of Health Services, endeavoured to control the outbreaks. By March 1972, the smallpox eradication headquarters had been re-established under Dr A. K. Joarder, Assistant Director of Health Services; divisional surveillance teams had been reconstituted and were endeavouring to detect and contain outbreaks as best they could. Smallpox continued to spread, however, and 4 WHO epidemiologists were hurriedly dispatched. Among them were Dr Stanley Foster, who had previously served as the chief smallpox adviser in Nigeria, and Dr Nilton Arnt, one of the principal epidemiologists who had worked in the eradication campaign in Brazil. Some 3800 temporary vaccinators were hired to perform vaccinations, primarily in the large temporary refugee camps and surrounding districts. At first the epidemic was largely confined to 3 south-western districts—Barisal, Faridpur and Khulna. Active search, however, revealed the presence of smallpox in 27 of the country's 57 subdivisions, although most had only a few cases. The refugees were mainly Hindus and initially the outbreaks afflicted Hindu areas and villages, but within a few generations of disease transmission, other groups were infected as well. In March, epidemic smallpox was detected in Khulna Municipality, the third largest city in Bangladesh. The control of smallpox in urban areas was recognized to be vital, and here a vigorous and remarkably successful programme was begun on 28 April (Sommer, 1974; Sommer & Foster, 1974). Eight 4-man surveillance teams were organized and trained to identify infected cases through interviewing patients at the Infectious Disease Hospital and by visits to the bazaars. When a case was found in the city, all persons in the household and compound were vaccinated and house-to-house searches were conducted throughout the village or bustee. The area was revisited after 2 or 3 days and again 3 weeks later to vaccinate individuals who had been missed during the first visit and to be certain that transmission had stopped. Containment measures were necessarily limited in scope because of the paucity of staff and the extent of the epidemic. In fact, it was

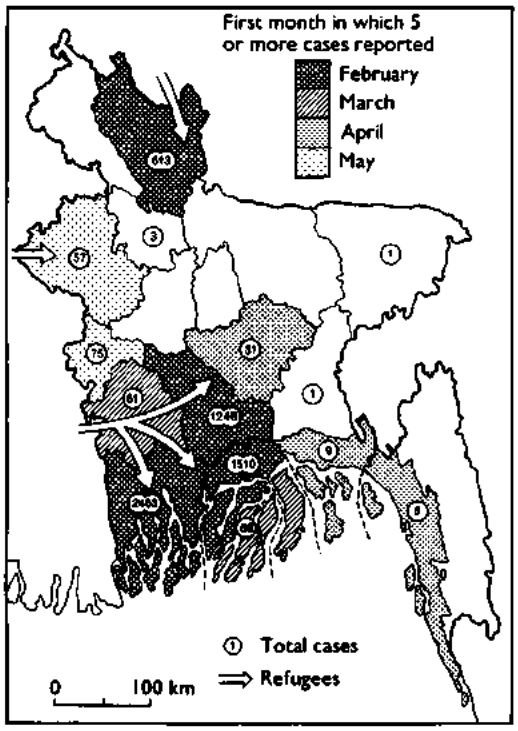


Fig. 16.8. Bangladesh: infected districts and number of reported cases of smallpox as of 30 June 1972.

necessary to divide the city into 3 segments and to deal with each in turn. Although 1073 cases were detected, smallpox was effectively contained within a matter of 4–6 weeks in each of the areas (Fig. 16.6). Meanwhile, the disease had broken out in a city refugee camp housing 30 000 persons. It was decided to vaccinate everyone in the camp by the simple expedient of making vaccination a prerequisite for the receipt of relief supplies. Altogether 233 cases were detected; however, the outbreak was as successfully dealt with as the one in Khulna Municipality (Fig. 16.7). To have achieved so much so quickly, with so few health personnel, at a time of considerable civil turmoil was a remarkable accomplishment and encouraged staff in the belief that the flood of importations might yet be successfully contained.

However, smallpox was spreading rapidly through rural as well as urban areas, wherever returning refugees settled. A survey of one rural *thana* in May revealed 2298 cases among 250 000 inhabitants—approximately 1 case per 100 population. Meanwhile the disease continued to spread through refugee resettlement camps, some of which housed Bangladeshis of Bihari origin. From these camps, it spread to adjoining *thanas*. Small outbreaks developed in Dhaka and Chittagong but these were controlled. Intensive studies of a number of the outbreaks in which cases and deaths were thoroughly investigated revealed case-fatality rates of up to 28%, higher than those found elsewhere in the subcontinent and undoubtedly reflecting the extensive malnutrition then prevailing.

By the end of June 1972, 6144 cases had been reported in Bangladesh, of which 5834 (95%) were from only 4 districts (Fig. 16.8). Although reporting was recognized to be incomplete, it sufficed to indicate that large parts of the country had few or no cases. With a concerted effort such as had been made in Khulna and conducted throughout the monsoon period of diminished transmission, the staff hoped that the epidemic spread could be contained. Special assistance was given to the programme by the United Nations Relief Operation, Dacca, in the form of motor vehicles, boats, outboard engines and bicycles. WHO provided motor cycles and additional bicycles to facilitate the effort (Table 16.8). However, much of the transport served only to replace that which was worn out or had been destroyed during the civil war.

Of the 4 WHO epidemiologists who had assisted during the spring emergency, Dr Arnt and Dr Foster continued on permanent assignment in what proved to be one of the most arduous and taxing endeavours of the global eradication programme. They were soon joined by 3 other staff, who remained with the programme essentially full time

Table 16.8. Bangladesh: transport provided to the smallpox eradication programme, 1967–1975

	1967–1971	1972–1973	1974	1975	Total
Motor vehicles	49	34[a]	0	35	118
Motor cycles	183	110	50	165	508
Boats	25	10[a]	0	8	43
Outboard engines	28	11[a]	20	31	90
Bicycles	1 500	750[a]	2 370[a]	300	4 920

[a] Supplied by the United Nations Relief Operation, Dacca.

Plate 16.5. Harkishan D. Mehta (b. 1934), a WHO epidemiologist with the Bangladesh programme, 1974–1978, on the left, with Stanley O. Foster (b. 1933), a United States epidemiologist who had previously served as senior adviser to the smallpox eradication programme in Nigeria, 1966–1972, then served in Bangladesh as a WHO adviser for smallpox eradication, 1972–1977.

until transmission had been interrupted: Dr Nicholas Ward, who had previously been employed as a District Medical Officer in Botswana; Dr Stanley Music, a Bengali-speaking epidemiologist who had previously been stationed in Dhaka on assignment from the Communicable Disease Center; and Dr Daniel Tarantola, a physician who had been working at a hospital in northern Bangladesh with a French voluntary organization.

THE PROGRAMME IS RE-ESTABLISHED, JUNE 1972–SEPTEMBER 1973

The reporting system, which required weekly telegraphic reports from each of the 57 subdivisions, was reinstituted in March 1972 (Foster et al., 1980). Reports to the subdivisions were provided through *thana* sanitary inspectors by government health assistants, each of whom worked in a union, the health assistant/population ratio being approximately 1 to 15 000. During the summer, 4-man surveillance teams, headed by a sanitary inspector, worked in each infected subdivision; in each infected *thana*, vaccinators were grouped into 3-man teams for active search and containment. Particular emphasis was placed on the search in weekly markets by health workers using megaphones. This approach was later shown to detect approximately 80% of all outbreaks within an area of 65 square kilometres.

A mass vaccination campaign in the 4 most heavily infected districts had begun in the spring, but was stopped when it became apparent that it would accomplish little more than the 1970 campaign. As Dr Huq and his colleagues stated in a report dated October 1972: "It is now clear that eradication through mass vaccination is not feasible ... The orthodox principle of blind, systematic vaccination has already been given up."

Between June and October 1972, 400–800 cases were detected monthly, a substantial number for that season of the year. However, up to the end of October, outbreaks had been documented in only 88 of the 409 *thanas* in the country, and by then only 36 were still infected. By the end of 1972, 10 754 cases had been reported, approximately one-tenth of the number which had actually occurred, as a survey for facial pockmarks carried out 4 years later was to show (Hughes et al., 1980; Fig. 16.9; Table 16.9). The system for detecting and reporting cases, although well designed, lacked adequate supervision.

After the monsoon, with the season of high transmission approaching, it was decided to concentrate resources in the subdivisions of the 4 most heavily infected districts. A 10-man team, headed by an assistant health inspector, was assigned to each of the infected *thanas* to search for cases and to contain any outbreaks that were found. A national surveillance team with 5 assessment staff supervised these efforts and made repeated visits to the sites of outbreaks to ensure that they had been contained. Four surveillance teams, working under the supervision of the national eradication headquarters, travelled throughout the areas which had reported only a few imported cases to strengthen surveillance and to contain outbreaks.

The strategy was based on the assumption that smallpox would tend to remain localized in the areas already identified as infected. A key factor in the strategy was the control of smallpox in Dhaka, the capital and largest city in the country, and the potential focus of spread of smallpox into the largely smallpox-free areas of central and eastern Bangladesh. In April and May 1972, 26 cases had occurred among refugees in Dhaka but the outbreaks

Table 16.9. Bangladesh: number of reported cases of smallpox as a percentage of the estimated number of cases (surveillance efficiency), 1972–1975[a]

Year	Number of reported cases	Estimated number of cases	Surveillance efficiency (%)
1972	10 754	91 415	11.8
1973	32 711	81 906	39.9
1974	16 485	33 390	49.4
1975	13 798	16 628	83.0
Total	73 748	223 339	33.0

[a] From Hughes et al. (1980).

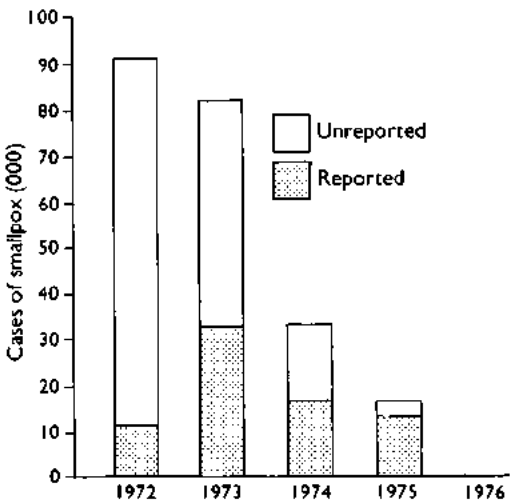


Fig. 16.9. Bangladesh: estimated total number of smallpox cases that occurred compared with the number of cases reported, 1972–1976.

Table 16.10. Dhaka Municipality: number of reported cases of and deaths from smallpox, by month, 1972–1973[a]

Month	1972		1973	
	Number of cases	Number of deaths	Number of cases	Number of deaths
January	0	0	633	380
February	0	0	1 550	991
March	0	0	2 379	1 409
April	8	0	253	608[b]
May	18	3	72	115
June	0	0	14	49
July	1	0	2	7
August	1	0	3	0
September	0	0	0	0
October	29	9	1	1
November	80	24	0	0
December	216	84	0	0
Total	353	120	4 907	3 560

[a] From Joarder et al. (1980).
[b] Including deaths related to cases reported in previous months.

were contained. Only a single case was recorded in July and another in August, but early in October scattered outbreaks began to occur in densely populated urban slum areas and resettlement camps, in which the night-time population densities were estimated to be as high as 195 000 per square kilometre, or 1 person to every 5 square metres. Twenty-nine cases were detected in October, 80 in November and 216 in December (Table 16.10). The containment of outbreaks in the densely congested areas seemed all but impossible short of an area-wide mass vaccination campaign.

In January 1973, Dr Ward assumed responsibility for the development of a special programme in Dhaka to control smallpox more rapidly. A municipal headquarters was established and 18 mobile surveillance units were formed.

● The Infectious Disease Hospital and the major graveyards of the city were visited daily to collect information on smallpox cases and deaths.

Table 16.11. Bangladesh: number of reported cases of smallpox, by division and by month, 1972–1973

Month	Chittagong	Dhaka	Khulna	Rajshahi	Total
1972:					
January	0	0	0	0	0
February	0	59	165	248	472
March	1	218	548	59	826
April	15	547	437	20	1 019
May	0	382	2 574	343	3 299
June	1	73	451	3	528
July	3	139	544	64	750
August	13	237	400	27	677
September	3	189	189	58	439
October	9	81	308	10	408
November	33	508	504	272	1 317
December	92	234	546	147	1 019
Total	170	2 667	6 666	1 251	10 754
1973:					
January	374	1 484	1 611	450	3 919
February	534	2 521	1 838	389	5 282
March	489	2 012	1 926	852	5 279
April	528	1 905	1 777	1 543	5 723
May	372	1 027	1 068	1 710	4 177
June	247	672	910	954	2 783
July	51	157	214	187	609
August	101	425	464	330	1 320
September	19	279	255	110	663
October	106	259	170	111	646
November	12	496	237	198	943
December	62	637	234	404	1 337
Total	2 895	11 874	10 704	7 238	32 711

● Fixed check-points were established at transport terminals to collect information and to vaccinate passengers.
● Vaccination of the inhabitants of slum areas and refugee centres was carried out at night as well as during the day.

During 1973, 1 747 000 vaccinations were performed in Dhaka City alone, but the epidemic did not begin to abate until April. Although only 4907 cases were detected, it was apparent from the large number of deaths attributable to smallpox that there were many more cases than this—an estimated 14 000 or more.

Meanwhile, during the spring of 1973, 26 surveillance teams worked throughout the country; 5 of these were national teams each with responsibility for a region, 9 were district teams, 4 were municipal teams and 7 were assigned to the heavily infected subdivisions. Each team moved from *thana* to *thana* searching for cases in major markets, schools and selected villages. When an outbreak was discovered, local health staff were mobilized to vaccinate the residents of the 30 houses nearest to those with cases.

The programme staff worked frantically to contain the outbreaks but, with Dhaka heavily infected, smallpox quickly spread across Bangladesh. The number of reported cases increased from only 1019 in December 1972 (Fig. 16.10) to 3919 in January 1973 and to 5282 in February; in February, cases were reported from every district in the country (Table 16.11).

The epidemic reached its peak in April and once again began to subside with the onset of the monsoon. The number of reported cases was substantially greater than during the preceding year, but since the number of surveillance teams had increased and notification was more complete, it was hoped that during the monsoon season transmission could be brought under control. To facilitate this, containment procedures were changed, since it was found that outbreaks were persisting because of failure to vaccinate household contacts who were absent during the day. Accordingly, each team was required

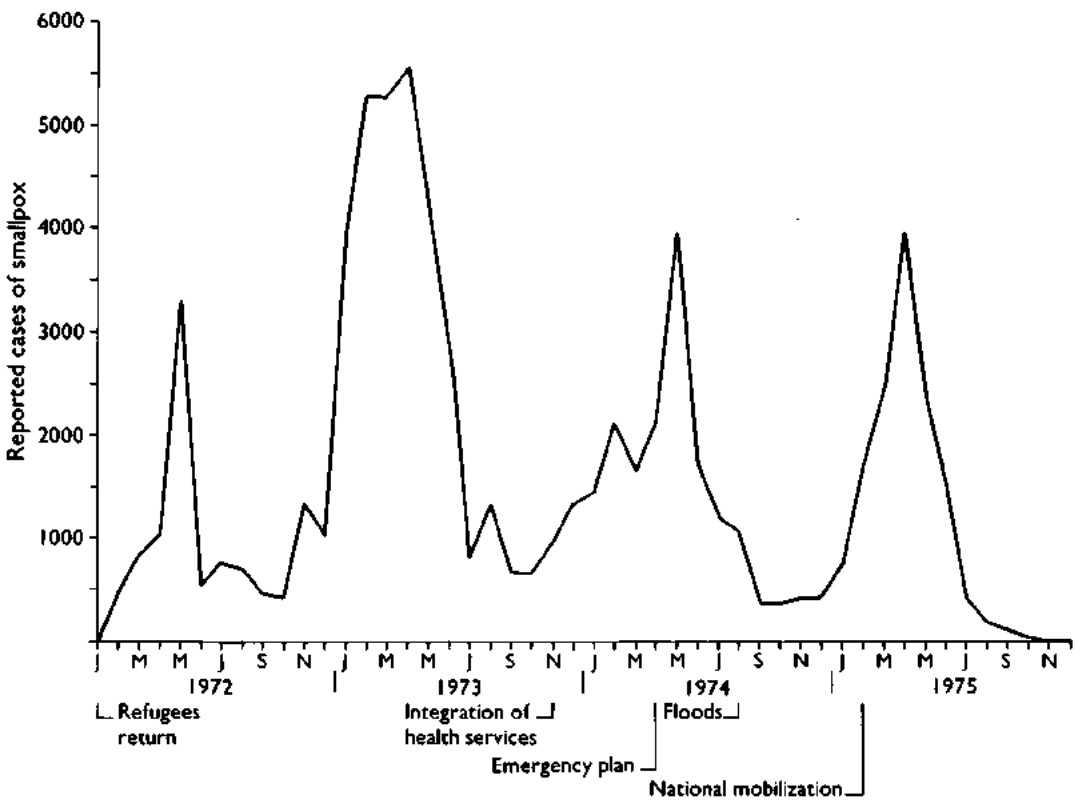


Fig. 16.10. Bangladesh: number of reported cases of smallpox, by month, January 1972–December 1975.

Table 16.12. Bangladesh: number of infected villages, by district and by month, 1974–1975

Division/district	Population (thousands)[a]	1974											
		Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Dhaka:													
Dhaka	8 875	15	25	17	26	19	7	4	3	1	4	5	5
Faridpur	4 735	22	10	17	27	20	8	5	6	1	0	0	0
Mymensingh	8 825	103	173	312	382	342	257	232	149	78	51	62	97
Tangail	2 425	0	15	19	24	20	23	5	12	6	3	2	0
Khulna:													
Barisal	4 580	3	4	4	1	1	0	0	1	0	0	0	0
Jessore	3 880	8	14	10	13	3	0	2	0	0	0	0	0
Khulna	4 150	4	11	15	15	8	1	0	0	0	0	0	0
Kushtia	2 195	4	11	10	2	1	0	0	0	0	0	0	0
Patuakhali	1 750	6	35	33	10	9	10	6	3	1	0	0	0
Chittagong:													
Chittagong	5 025	0	0	0	0	0	0	1	3	3	1	0	0
Chittagong Hill Tracts	590	0	0	0	0	0	0	0	0	0	0	1	0
Comilla	6 785	1	2	5	2	1	1	1	1	2	2	0	1
Noakhali	3 770	1	2	1	0	0	0	0	0	0	1	0	0
Sylhet	5 550	15	12	10	2	2	7	2	10	13	2	2	0
Rajshahi:													
Bogra	2 600	42	44	50	43	39	11	8	8	4	0	1	12
Dinajpur	3 000	2	13	18	19	37	17	17	11	7	1	1	9
Pabna	3 185	3	3	6	5	1	0	1	5	1	1	0	0
Rajshahi	4 975	46	38	69	100	120	111	75	29	8	3	0	0
Rangpur	6 350	34	110	157	278	245	124	87	39	30	22	56	99
Total	83 245	309	522	753	949	868	577	446	280	155	91	130	223

[a] Estimates calculated for 1977 as given by Joarder et al. (1980).

to carry out house-to-house vaccination in each infected village at night or in the early morning.

REORGANIZATION OF THE HEALTH SERVICES, OCTOBER 1973

In October 1973, only 646 cases were notified. Reports were being received promptly from 95% of the subdivisions and there was increasing confidence that few outbreaks were being missed. On the assumption of an average of 4 cases per outbreak, it was calculated that there were perhaps 150–175 infected villages in the entire country. Dhaka was free of smallpox, as were most subdivisions of Rajshahi and Chittagong Divisions. To ensure a closer supervision of activities throughout the country, programme staff decided in October to set up 25 district surveillance teams, 1 for each of 19 districts and an additional team for each of the 6 largest districts. Each team, which consisted of 5 persons, led by a health inspector, was given transport (a motor vehicle, a motor cycle or a boat).

The plan experienced a serious setback, however, when in November, the government decided to suspend health activities temporarily in order to reorganize the health services. The field staff of the hitherto autonomous malaria eradication programme were to be merged with other health workers into a single integrated health care service. The new workers were to be called "family welfare workers", each assuming responsibility for a specific geographical area containing approximately 5000 people. The tasks assigned to them included preparing individual family health cards, registering married couples and births, performing smallpox vaccination, searching for cases of malaria and smallpox, and distributing vitamin A capsules and contraceptives, as well as providing health education and family-planning materials.

The integration of all health services had long been a tenet of WHO but practical approaches to its accomplishment had never been satisfactorily elaborated. Bangladesh's experience did not provide a model. A training programme was hastily concocted and, for a period of 4 weeks, virtually all health staff

Table 16.12 (*continued*)

1975												Division/district
Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	
												Dhaka:
56	100	159	211	185	108	27	6	4	0	0	0	Dhaka
8	39	81	120	63	23	10	4	0	1	0	0	Faridpur
271	349	349	193	69	24	10	2	0	0	0	0	Mymensingh
2	8	15	17	15	3	0	0	0	0	0	0	Tangail
												Khula:
4	13	26	41	24	23	18	5	4	1	1	0	Barisal
0	0	1	11	16	7	1	0	0	0	0	0	Jessore
1	2	6	7	4	2	1	0	0	0	0	0	Khulna
0	0	7	30	13	8	2	0	0	0	0	0	Kushtia
0	0	1	3	1	1	0	0	0	0	0	0	Patuakhali
												Chittagong:
0	2	5	4	0	1	10	4	3	1	0	0	Chittagong
0	0	0	0	0	0	1	0	0	0	0	0	Chittagong Hill Tracts
7	40	78	99	108	46	7	0	5	0	0	0	Comilla
0	11	24	50	32	13	9	3	1	0	0	0	Noakhali
1	5	15	124	210	150	29	13	0	0	0	0	Sylhet
												Rajshahi:
65	108	205	215	95	22	1	0	0	0	0	0	Bogra
10	28	36	55	25	12	2	0	0	0	0	0	Dinajpur
0	1	3	12	17	9	0	1	2	0	0	0	Pabna
2	4	13	39	10	3	0	0	0	0	0	0	Rajshahi
145	127	108	54	32	14	0	0	0	0	0	0	Rangpur
572	837	1 132	1 280	948	476	131	38	19	3	1	0	Total

except smallpox surveillance teams were withdrawn from the field for training. They returned to the field to begin a whole range of new and unfamiliar activities for which few of the necessary supplies were provided. Their first task, which required some 2 months to complete, was to prepare a separate health card for each family on which the name and age of each family member were to be listed. Despite the integration of field staff, however, 2 separate supervisory structures were left in place: the malaria eradication programme structure and the previous health service structure. Former malaria eradication staff and health service staff looked to their respective former supervisors for direction. The entire health service, which had not been functioning well, deteriorated further; many employees abandoned their jobs and returned to cultivating their small plots of land.

All activities—case detection, containment and vaccination—sharply diminished after November, but despite less adequate reporting by the health staff the number of cases which were detected doubled between October and December. Smallpox cases, widely but sparsely distributed throughout the country immediately after the monsoon, suddenly began to occur in large numbers in the northern districts of Rangpur and Mymensingh (Fig. 16.11), both of which, up to then, had been free from the disease.

In December 1973, the surveillance system was modified to enumerate "infected villages" as well as the numbers of cases and deaths, a practice that had been adopted earlier in the year in several states of India. In Bangladesh, each village was designated infected until 6 weeks had elapsed after the onset of the last case. (India continued to use a 4-week interval until later that year.)

During the first 4 months of 1974, the number of infected villages increased from 309 in January to 949 in April (Fig. 16.12; Table 16.12). Rangpur and Mymensingh Districts accounted for 660 (69.5%) of the total. In April, Khulna Division, which had been the epicentre of smallpox after the return of the refugees, had only 41 infected villages. The concentration of resources and supervisory personnel in 1972–1973 in the initially heavily infected areas had been remarkably successful in stopping spread, but the programme in other areas had consequently received less attention. With the withdrawal of health staff from the field and

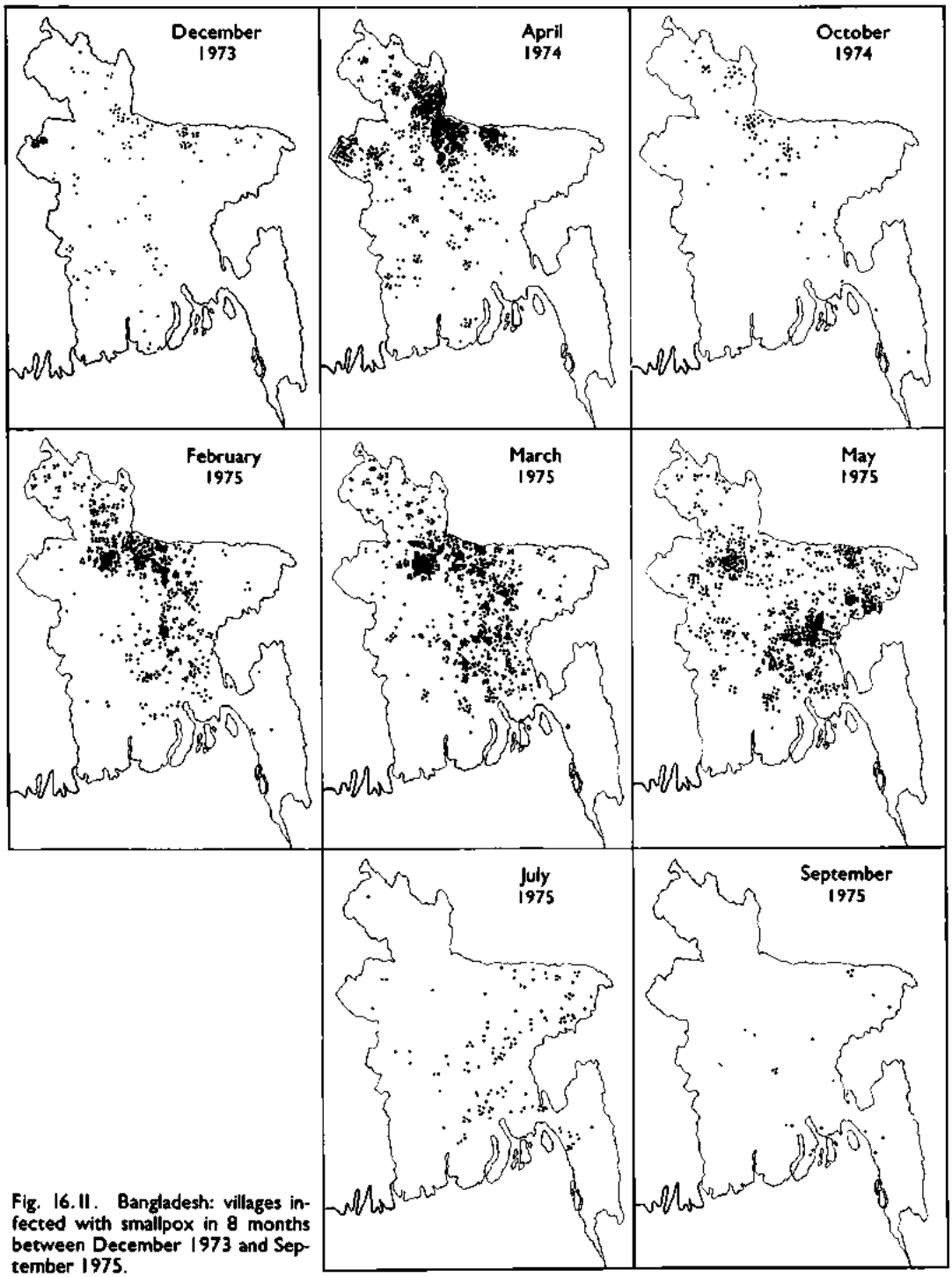


Fig. 16.11. Bangladesh: villages infected with smallpox in 8 months between December 1973 and September 1975.

Plate 16.6. **A**: Surveillance during the monsoon season was an especially arduous task as streams washed out roads, and foot-bridges often consisted of little more than a single bamboo pole. **B**: Alan H. Schnur (b. 1948) served as a US Peace Corps volunteer with the smallpox eradication programme in Ethiopia from 1971 to 1974 before being recruited as a WHO consultant for service in India and Bangladesh.

the subsequent confusion accompanying the reorganization of health services, a potentially manageable situation had developed into a major problem.

AN EMERGENCY PLAN FOR SMALLPOX CONTROL, APRIL 1974–JANUARY 1975

By April, it was apparent to everyone that the integrated health service scheme was achieving little. A redefinition of the responsibilities of supervisors and workers and of the management structure was required. Accordingly, on 9 April the government issued a detailed "Emergency Plan for Smallpox Eradication under the Integrated Health and Family Planning Programme", of which an important component provided for unified direction of the health services. Dr Mahboober Rahman, former director of the successful national malaria eradication programme, was asked to supervise all health activities, including smallpox eradication. Within the new administrative structure, responsibilities specific to smallpox eradication were defined. For operational purposes, new posts were created for staff at subdivision and *thana* levels. Civil surgeons, responsible for health matters in the subdivisions, were requested to appoint an area smallpox eradication officer for each of the 57 subdivisions and a *thana* smallpox eradication officer for each of the 424 *thanas*. In some areas, the incumbents were health services staff and in others malaria eradication staff. To assist family welfare workers in containment measures and to improve liaison with villagers, the order also authorized the temporary appointment and remuneration (6 *takas*, or about US$ 0.75, per day) of an emergency field worker for each outbreak. The field workers were to be recruited and trained in the villages. The employment of emergency field workers afforded an unexpected bonus in that they provided temporary accommodation in the villages for smallpox programme staff.

When a case of smallpox was discovered in a village, the family welfare worker was to cease other duties and initiate containment, with the help of the emergency field worker, and to inform his supervisors. The family

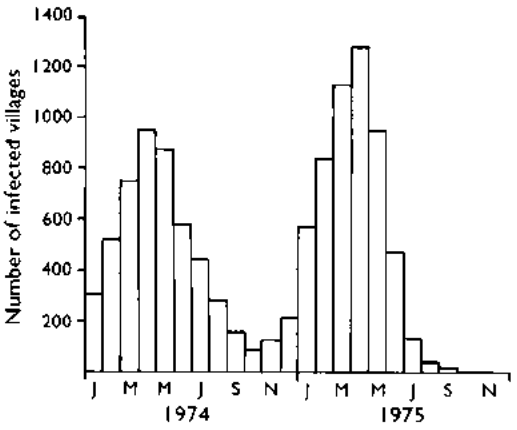


Fig. 16.12. Bangladesh: number of smallpox-infected villages, by month, 1974–1975.

welfare worker was to reside in the infected village for not less than 10 days and to vaccinate all its residents as well as all persons living within a half-mile (800 metres) radius. The newly designated *thana* smallpox eradication officers were given the responsibility for organizing and coordinating all outbreak containment programmes. The area smallpox eradication officer was required to visit each *thana* not less than once a month and to send a weekly progress report to Dhaka.

A monthly national meeting of all area smallpox eradication officers was instituted to review progress and to decide on plans for the next month. As was the case in India, the meetings proved to be especially valuable in motivating staff, in providing continuing education and in allowing for an ongoing appraisal of progress and any necessary redirection of the programme.

Each week an epidemiological report of newly detected cases and deaths was compiled at the subdivision level and sent by telegram to the national headquarters. A more detailed written report was prepared every month.

Provision needed to be made for the isolation of patients in the densely crowded areas of Bangladesh. Here it was a more difficult problem than in many other parts of the subcontinent. In rural areas, the patients could be isolated in their houses, but in the urban slums and in refugee resettlement camps, they had to be isolated in a special facility. In the cities and towns of Khulna, Chittagong, Sylhet, Rajshahi and Dhaka, there were infectious diseases hospitals which provided for the isolation of cases but, as elsewhere, they more often became centres for the dissemination of smallpox. Hospital superintendents rarely ensured that patients and visitors were vaccinated on entry. Consequently, smallpox eradication programme staff were obliged to organize and staff vaccination check-points at each hospital, sometimes with local police support. In heavily populated areas in which there were no hospitals, isolation wards or camps were set up in government buildings or even in tents, if necessary.

With 10 500 family welfare workers in the field, a defined supervisory and reporting structure, 25 special motorized surveillance teams, and 12 WHO epidemiologists, it seemed all but certain that transmission would be interrupted during the monsoon and post-monsoon period. Just 4 years previously, with far fewer surveillance teams, assisted by only 2 WHO epidemiologists, and a much less effective reporting system, transmission had been interrupted in less than 6 months.

The number of infected villages fell steadily, from 949 in April to 280 in August, of which 217 (78%) were in the northern districts of Rangpur, Rajshahi and Mymensingh. Even the distribution of the remaining outbreaks, similar to the pattern in 1970, suggested that the situation in 1974 might replicate that obtaining in 1970. The number of cases being detected remained high—1069

WHO/L. DALE, 1975

Plate 16.7. Mahboober Rahman (b. 1933), formerly director of the national malaria eradication programme, assumed overall direction of the integrated health programme in April 1974 and brought order to a chaotic administrative structure.

in August compared with 2110 in April (Table 16.13)—but detection was occurring earlier and more than 50% of all outbreaks consisted of only 1 or 2 cases. As an incentive for family welfare workers to report cases, it was decided in August to offer a reward of 50 *takas* (about US$6.50) to anyone who detected an outbreak. The system had proved successful in many states of India and its application at this time in Bangladesh seemed

PEOPLE'S REPUBLIC OF BANGLADESH-MINISTRY OF HEALTH AND FAMILY PLANNING-INTEGRATED HEALTH SERVICES-SMALLPOX ERADICATION PROGRAMME

AREA SMALLPOX OFFICER'S SMALLPOX MONTHLY REPORT

DISTRICT BOGRA AREA BOGRA MONTH MAY '74

1. Thana report of smallpox infected villages

Note: A village is designated as smallpox infected from date of detection until six weeks after the last date of attack at which time the village must be certified free by field visit of District level personnel (CS, CMCH, SDMCH, DMEO, ASO, Surveillance Team)

IF NO SMALLPOX INFECTED VILLAGES CHECK BOX /____/

THANA (LIST NAME OF ALL SMALLPOX INFECTED THANAS	NUMBER OF VILLAGES INFECTED 1ST OF MONTH	NUMBER OF (+) NEWLY DETECTED SP VILLAGES	NUMBER OF (-) SP VILLAGES CERTIFIED SP FREE	NUMBER OF (-) SP VILLAGES END OF MONTH	NUMBER OF ACTIVE CASES LAST VISIT
1. JAIPURHAT	1	0	1	0	0
2. SHERPUR	19	6	15	10	13
3. SHARIAKANDI	4	4	1	7	5
4. NANDIGRAM	0	0	0	0	0
5. KHETLAL	6	2	6	2	0
6. SHIBGANJ	5	1	4	2	1
7. SADAR	6	5	4	7	12
8. DHUNOT	0	10	3	7	2
9. GABTALI	2	4	2	4	3
10.					
11.					
12.					
TOTAL	43	32	36	39	36

2. AREA SMALLPOX OFFICER FIELD VISITS DURING MONTH

Number of visits to newly infected smallpox villages 28
Number of follow up visits to old smallpox villages 62
Number of visits to investigate villages where diagnosis of rash not smallpox Nil

Signed Area Smallpox Officer [signature] Date 10.6.74

Plate 16.8. Bangladesh: example of monthly smallpox report.

Table 16.13. Bangladesh: number of reported cases of smallpox, by division and by month, 1974

Month	Chittagong	Dhaka	Khulna	Rajshahi	Total
January	16	763	132	521	1 432
February	189	668	351	899	2 107
March	96	613	298	635	1 642
April	25	1 410	207	468	2 110
May	4	1 225	183	2 525	3 937
June	50	776	21	874	1 721
July	73	483	13	512	1 081
August	91	447	117	414	1 069
September	98	130	5	128	361
October	39	191	0	78	308
November	18	139	3	203	363
December	6	222	0	126	354
Total	705	7 067	1 330	7 383	16 485

appropriate. Additional help was provided by the United Nations Relief Operation, Dacca (UNROD), which was in the process of concluding its activities; it turned over to the smallpox eradication programme a central transceiver and 8 field radios. Six more field radios were added later and thus a valuable network of communication was established between the smallpox eradication programme headquarters and epidemiologists in the field.

In October 1974, only 91 infected villages remained, and periodic village-by-village searches were initiated. A similar search programme had begun in India a year before and more recently in Pakistan, but such searches in Bangladesh had not been possible before late spring because of the turmoil caused by the reorganization of the health services. During the monsoon months of 1974, national and WHO staff alike felt that searches were not required, in view of the existence of a unified health service and the assignment of a family welfare worker in each population unit of 5000 persons. Since each worker was expected to visit every house within his jurisdiction every 5 weeks and was motivated by the promise of a reward of 50 *takas* (about 5 days' pay) for the discovery of a case, it seemed unlikely that many outbreaks would be missed. The initiation of a search programme in October was intended as the first stage in the development of a scheme to confirm that transmission had been interrupted rather than as an operational tool to detect cases, as in India.

The late summer months, however, had brought still another tragedy to Bangladesh. The most extensive and severe floods for more than two decades swept through major

WHO / L. DALE

Plate 16.9. When isolation of smallpox patients in their own houses was not possible, hospitals were used, some of which were specially constructed, as was this one in Sylhet District.

An Episode Indicative of Frustration and Misguided Effort

The climate of feeling in Bangladesh oscillated between optimism—that the interruption of transmission was only months away, an opinion prevailing in October and November 1974—to profound pessimism and doubt that eradication could ever be achieved. The early months of 1975 represented an extreme of the latter mood. Frustration and exasperation sometimes compromised judgement, as was exemplified in Bogra, a municipality and district in north-central Bangladesh.

By the autumn of 1974, Bogra District, once heavily infected, had interrupted smallpox transmission at the conclusion of a thoroughly competent but exhausting campaign. However, in late December 1974 and in January 1975, outbreaks began to recur following importations from the famine-stricken area to the north, and cases were detected in the municipality. The smallpox eradication staff were concerned about the prospects of wide dissemination of smallpox from an urban area and decided that a mass vaccination campaign throughout the city was urgently required. While such a scheme might seem attractive, similar efforts in the past had always proved costly in time and manpower and were rarely successful, in part because of the continual migration of the population. Following a 10-day house-to-house mass campaign, assessment revealed that only 50% of the inhabitants had been vaccinated. A second campaign proved no more successful. Yet a third campaign was organized, this time employing 3 WHO advisers who had been withdrawn from supervision of outbreak containment in rural areas. During the course of 2 weeks, with the staff working 15 hours a day, 7 days a week, a coverage of 93% was finally achieved. No sooner had this task been completed than a major privately sponsored fair opened which drew upwards of 20 000 visitors per day. Thenceforth outbreaks began to recur throughout the district, of which most could be traced to contact with infected persons at the fair. Efforts were made to persuade the organizers of the fair to close it down or to allow all those attending it to be vaccinated when they bought their tickets. The entrepreneurs, however, were also the principal civic officials and they were not anxious to discourage attendance by making vaccination a requirement. Six weeks of discussion were to elapse before the fair was finally closed by order of the central government. By then, Bogra was the world's second most heavily infected district. Not until May did smallpox begin to subside.

parts of the northern districts, where most of the remaining infected villages were located. Some refugees began to move from the area at that time, but in November and December, the season when crops were usually harvested, severe famine struck.

During the first week of October, only 24 cases were detected, but in succeeding weeks the numbers began to increase sharply. By mid-December, there were 168 infected villages, of which only 23 were outside the two flood-afflicted districts, but 20 outbreaks had occurred as a result of spread from these districts. Outbreaks were being detected unusually rapidly—55% within a week of onset and 88% within 3 weeks. The containment of outbreaks was not optimum but, still, in 84% of them no cases were detected more than 21 days after the onset of the first case.

Because of population movement and crowding, however, smallpox spread explosively. In Rangpur District, a beggar living in a market-place died of smallpox on 2 December; 48 second generation cases in 18 villages occurred among those who had visited the market. In Faridpur District, south of Dhaka, a fatal case in a village was the source of 37 second generation cases in 4 different villages (WHO/SE/74.65, Rangaraj & Yusuf). In mid-December, cases were discovered among famine-stricken refugees in Dhaka and in the district towns of Bogra and Mymensingh. Efforts to control the spread of smallpox among refugees sleeping shoulder to shoulder in the extensive slum areas of the cities was an all but impossible task.

The occurrence at this particular time of the most widely celebrated Muslim holiday,

Plate 16.10. Increasing numbers of staff and additional resources were provided to the programme in Bangladesh during 1974–1975 in a final intensive effort to eradicate smallpox from Asia. **A**: Andrew N. Agle (b. 1937), a veteran of smallpox eradication programmes in western and central Africa, 1966–1971, then in Afghanistan, 1972–1974, was the WHO administrative officer in Bangladesh. **B**: Jane Brown (b. 1942), seconded from WHO Headquarters for 6 months, directed radio communications. **C**: CARE, a private charitable organization registered in the USA, built an operations building, "Smallpox Zero", to house additional programme staff. Additional buildings were constructed for the storage of parts and a garage for maintenance of a new fleet of Indian-made Jeeps.

the *Eid* festival (*Id ul Fetre*), further compounded the problem, since this feast was the occasion for large family gatherings, entailing extensive travel.

Meanwhile, in Nepal and Pakistan, transmission had been interrupted; in India, the incidence of smallpox and the number of infected villages were declining steadily. It became increasingly apparent that the course of events in Bangladesh would determine the success or failure of the endeavour to eradicate smallpox from Asia. Additional international staff were assigned to strengthen the programme in Bangladesh, the number increasing from 8 in June 1974 to 21 in January 1975. But smallpox continued to spread. As has already been mentioned, only 91 villages were infected at the end of October, but the number had increased to 130 by the end of November, to 223 by the end of December, and to 572 by the end of January. This last number was almost twice the figure recorded for the corresponding period one year earlier.

A catastrophe from the viewpoint of smallpox eradication occurred when the government decided that urban bustees should be demolished. In a matter of a few weeks, bulldozers and police dispersed an estimated 50 000–100 000 additional refugees from the cities throughout the countryside. Some had smallpox or were then incubating the disease. A frustrated, demoralized staff was called upon to regroup and to mount yet another national effort.

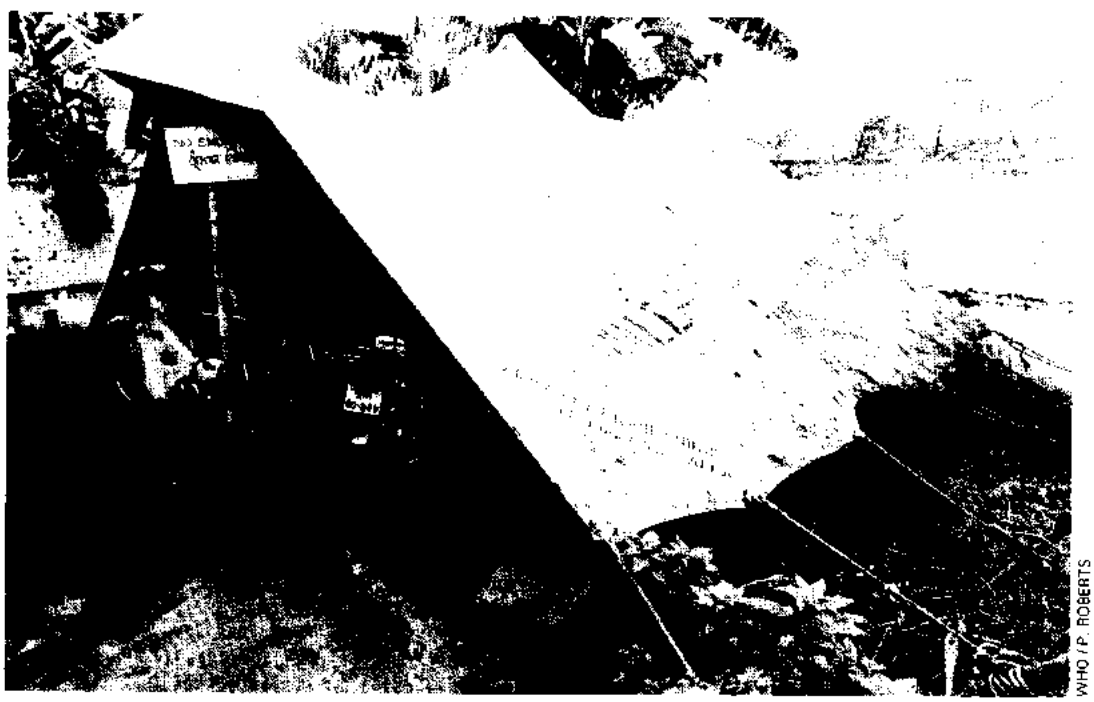
NATIONAL MOBILIZATION FOR SMALLPOX ERADICATION, FEBRUARY 1975

Beginning in December 1974, national health personnel and WHO staff stationed in Bangladesh, New Delhi and Geneva met repeatedly to decide on a revised strategy and additional measures that might be taken. With the extensive continuing movement of population, it was apparent that efforts would need to be greatly intensified, and that substantial additional funds would be required. However, WHO's Voluntary Fund for Health Promotion, as well as discretionary funds in the WHO regular budget, had been exhausted in strengthening the programme in India. Additional support would have to be sought, but this would require the approval by the Bangladesh Planning Commission of a revised plan of operations and the concomitant financing. Although the Secretary of Health and the WHO Representative in Bangladesh supported the programme, they were of little help. Both were adamant that eradication could be achieved only through a national mass vaccination campaign conducted through the basic health service structure. They were not persuaded by the argument that this would be futile in an already well vaccinated population, nor could they accept the fact that the newly created basic health service structure had all but ceased to function. Fortunately, the recently appointed principal health adviser to the Planning Commission, Dr Mohammad Ataur Rahman, had a far better and more realistic understanding of the problem and the resources needed. Dr Rahman was a knowledgeable and skilful administrator and virologist who had played a key role in the development of smallpox vaccine production in Dhaka, and subsequently had closely followed the progress of the eradication programme. Through his efforts, the Planning Commission was persuaded to direct an appeal for assistance to a number of international agencies. The Swedish International Development Authority responded—as it had in India—most rapidly and generously, making available US$ 3.5 million. Significant contributions were also made by Canada, Denmark, Norway and the United Kingdom.

In February 1975, a presidential directive was issued which declared smallpox to be a national emergency and ordered the mobilization of all available resources to assist in its eradication. Thirty-five Jeeps of Indian manufacture were hurriedly procured and driven to Bangladesh; others were loaned from other programmes. Additional radios, motor cycles, boats and outboard motors were obtained. Mr Rodney Hatfield, a young volunteer from OXFAM (a charitable organization registered in the United Kingdom), assumed responsibility for transport maintenance and repair; an old garage was transformed into a fully equipped workshop with a staff of 12 mechanics; and numerous Ministry of Health vehicles that had long been in disrepair were made roadworthy. An operations building was rapidly constructed by CARE (a charitable organization registered in the USA), using a new technique of jute and fibreglass construction. To coordinate field operations, WHO's former senior smallpox adviser in Afghanistan, Dr A. G. Rangaraj, joined the

P. CLAQUIN

A



WHO / P. ROBERTS

B

Plate 16.11. **A**: Small motor cycles were very useful for travelling around the country as they used little petrol, could be readily carried on boats and could be used on the narrow footpaths connecting villages. **B**: The smallpox programme motor park in Rangpur District in September 1975.

Table 16.14. Bangladesh: average numbers of international staff[a] and national epidemiologists employed in the smallpox eradication programme, by 3-month period, 1972–1977[b]

3-month period	1972	1973	1974	1975	
	International	International	International	International	National
January–March	5	3	9	41	0
April–June	4	5	10	68	5
July–September	2	6	11	64	25
October–December	2	7	14	40	25

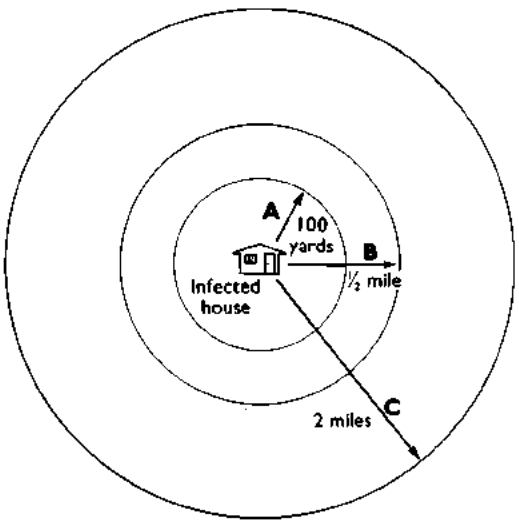
[a] In all, 207 international staff from 28 countries served in Bangladesh at some time during this 4-year period.
[b] From Joarder et al. (1980).

staff. Dr Stephen Jones and Dr Donald Francis came from India to assist in adapting the most effective techniques employed there to conditions in Bangladesh.

Numerous other WHO staff and consultants were urgently recruited from countries around the world (Table 16.14), many of them having served in Africa, South America and other parts of Asia. It was a group remarkably diverse in nationality, being composed of Brazilian, British, Czechoslovak, Egyptian, French, Soviet, Swedish and Swiss citizens. The Center for Disease Control and OXFAM were especially helpful in recruitment. New colleagues arrived every 2 weeks, to rendezvous in New Delhi for a Monday briefing. On Tuesday they flew to Dhaka and over the next 3 days received intensive field and classroom training before being dispatched to the field. Because there was a shortage of hotel accommodation, a house was leased which could accommodate 18 persons—unofficially called WHOSE House (an acronym for World Health Organization Smallpox Eradication). By May, 71 international staff were working in the field, and during that month the recruitment of Bangladeshi epidemiologists from universities and other settings was initiated.

A formidable challenge was presented by the administrative coordination and financial monitoring of a programme which, operating with US$12 000 a month in September 1974, was spending US$125 000 a week by February 1975. This daunting task was capably handled by Mr Andrew Agle, who had served in the western Africa and Afghanistan eradication programmes and had joined the Bangladesh programme staff in September 1974. He and Mr A. Alim Mia, a Bangladeshi administrator

Plate 16.12. WHO consultants. **A**: Pierre P.L. Claquin (b. 1947), a French epidemiologist, engaged for 3 months in March 1975, eventually spent a total of 27 consultant months in Bangladesh. **B**: T. Stephen Jones (b. 1941) was one of the many epidemiologists provided to WHO by the Centers for Disease Control in the USA. He served for 3 months in India in 1974 before spending 3 months in Bangladesh in 1975.



Infected house
Isolate patient
Enumerate and vaccinate residents and visitors
Twice-daily inspection for fever and rash
House guards (24 hours)

Zone A (100 yards)
Enumerate and vaccinate residents and visitors
Twice-daily inspection for fever and rash

Zone B (100 yards to ½ mile)
Enumerate and vaccinate residents
Daily house check for fever and rash

Zone C (½ mile – 2 miles)
Check every 5 days for fever, rash, or smallpox information

Fig. 16.13. Bangladesh: containment of smallpox outbreaks.

who had served with the programme since its inception, dealt with a considerable array of problems, both expected and unexpected. One of the more vexing was that of disbursing funds to the field epidemiologists for the payment of temporary staff to cover board and lodging, as well as petrol and repairs. The telegraphic transfer of funds to bank branches in peripheral areas would have been the most logical way of coping with the problem, but was technically impossible for many months. The only workable alternative approach was to disburse the funds at monthly meetings of supervisory field staff. However, the largest banknote then available was a 10-*taka* note (about US$1.25) and, during the intensive period of activity, field staff were receiving 30 000 *takas* or more each month. The inevitably large bundle of banknotes was difficult to handle, but the problem was solved by using capacious gunny sacks and carrying them into the field tied to the back of a motor cycle; although there was no attempt at concealment, thefts never occurred.

Under the national mobilization plan, and with many additional field epidemiologists available, containment measures were greatly expanded from previous strategies which called for one family welfare worker and one emergency field worker to vaccinate everyone living within a half-mile (800-metre) radius of each case. The containment measures were basically the same as those that had evolved in India.

A worker who discovered a case was instructed to isolate the patient immediately and to vaccinate all household members. A resident supervisor was appointed, usually the health worker in the area, who recruited 4 house guards responsible for keeping the patient in the house and for vaccinating all visitors. Food and water were provided if needed. (For the recording of activities, special "house guard books", such as had been used in India, were introduced in April.) The resident supervisor then hired 4–6 emergency field workers at 6 *takas* each a day. He trained them to register and vaccinate all residents and visitors within a half-mile radius of the infected house, and to search for cases in all markets, schools and houses within a 2-mile (3.2-kilometre) radius (Fig. 16.13). When these tasks were completed, the workers revisited all persons within the half-mile radius to detect and vaccinate any newcomers or others who had been missed during the intensive vaccination phase.

Resident supervisors were provided with a "containment book" in which the following information was recorded:

- a list of patients and the stage of their illness;
- information pertaining to the source of infection and contacts of the cases;
- a list of household members and temporary residents of Zones A and B (i.e., those living within a 100-yard (90-metre) and a half-mile (800-metre) radius, respectively, of the infected house);
- a list of staff and work schedules for all involved in containment;

Dr A. B. M. Kamrul Huda

Dedication and sacrifice were characteristic of many who served the programme, and a few gave their lives. One young medical officer who did so was serving at the time as the Subdivisional Medical Officer of Health in Chittagong. He was notified late one night of possible smallpox on an offshore island and arose early the next morning to take a ferry to the island. Because of high winds the ferry was cancelled. Dr Huda was anxious to investigate the rumour and took a small local boat instead. The boat capsized en route and Dr Huda drowned. He died on 3 March 1975, leaving a wife and two young children.

- a record of visits of supervisory staff from *thana*, subdivision and district levels;
- a map of the outbreak area showing each house, all houses being numbered;
- a record of all financial transactions—e.g., payments to emergency field workers for petrol, etc.

Check-points were set up on strategic paths and roads to collect information about other areas in which cases might exist and to vaccinate passers-by.

The source of infection of each case was examined and all possible contacts were vaccinated. Any contact with fever was isolated and members of the household were vaccinated. Whenever the suspected source of infection was in another *thana*, or whenever a contact had left the village for another area, a special message (cross-notification) was sent by messenger, telegram or radio. District, subdivisional and *thana* officers, surveillance teams and epidemiologists made periodic surprise visits to assess the efficacy of the work.

At the monthly meetings of supervisory field staff, problems were reviewed and procedures changed as required. An example of an unexpected event was the discovery by a Bangladeshi epidemiologist, Dr M. A. Sabour, that in 11 out of 17 outbreaks for whose containment he was responsible, cases were recorded 15 days or more after containment had begun. As he discovered, most of the cases were relatives of patients and should have been identified and vaccinated. He learned, however, that when a family in an infected home was asked to give the names of all recent visitors, they omitted to mention the names of relatives—since relatives, in their culture, were not considered to be visitors. The steady improvement of containment could be measured by the diminishing proportion of outbreaks in which cases occurred more than 15 days after detection of the outbreak (Fig. 16.14). In November, cases occurred in 27% of the outbreaks more than 15 days after detection; by June, the proportion was less than 10% (Foster et al., 1980).

With increasing numbers of epidemiologists in the field to investigate the source of outbreaks, to trace contacts who might have left the scene of an outbreak and to discover rumours of outbreaks as yet undetected, many possible additional cases were identified in more distant areas. The radio network was used extensively to forward such information for other staff to investigate. Beginning in February 1975, each cross-notification was recorded and the results of the field investigations were tabulated (Table 16.15). Between February and December 1975, 1468 cross-notifications were transmitted, leading to the discovery of 28 previously unknown outbreaks—not a large yield for the number of reports transmitted and investigated but important, nevertheless, in hastening the interruption of transmission. Three addi-

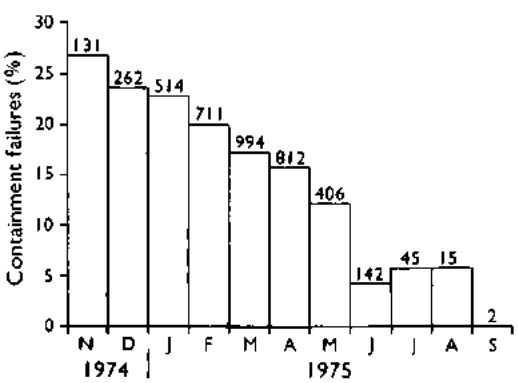


Fig. 16.14. Bangladesh: number of smallpox outbreaks per month, November 1974–September 1975, and the proportion with cases occurring 15 days or more after the outbreak was detected and in which containment measures were considered to have failed.

Table 16.15. Bangladesh: cross-notifications of suspected cases of smallpox within the country, 1975

Month	Number of reports transmitted	Smallpox[a]		Investigation result[a]			
		New outbreak	Known outbreak	Chickenpox	Other diagnosis or no disease	Case not found	No report
February	91	..	..	..	..	..	..
March	146	9	15	..	..	..	..
April	72	..	..	..	..	..	..
May	104	7	14	1	58	10	14
June	129	5	15	15	73	12	9
July	134	5	11	16	86	11	5
August	233	2	10	32	133	28	28
September	294	0	1	37	134	50	72
October	103	0	0	0	93	0	10
November	86	0	0	0	77	0	9
December	76	0	1	0	62	1	12
Total	1 468	28	67	101[b]	716[b]	112[b]	159[b]

[a] .. = data not recorded.
[b] Totals for May–December only.

tional outbreaks were discovered through notifications received from India.

SPECIAL SEARCH PROGRAMMES

A special 6-day village-by-village search for cases had first been organized in October 1974 and a second was conducted in December of that year. It was believed that if the family welfare workers could be carefully instructed to perform well only one of their many assigned functions—i.e., that of smallpox case detection during a 6-day tour of their area—the results would be better than if this activity were but one of the numerous tasks required of them. *Thana* supervisors reported that the searches in October and December were reasonably successful but assessment by district and subdivision staff and surveillance teams indicated that there were large areas in which no search had been carried out and few in which searches had been conducted competently.

With additional staff to assist in supervision, some of whom had had experience with this technique in India, more energetic search programmes were introduced in April 1975; these were repeated every 4–6 weeks. Approximately 14 500 staff were engaged in each search, following special training programmes at each operational level.

The workers were asked to visit markets, tea-stalls and every 20th house. They were instructed to show the smallpox recognition card at each location, and ask the viewers whether they recognized the disease—which most of them did. The health workers were told to inform their audience of the reward for reporting an unknown case of smallpox and where to report it; to record any information obtained about persons with rash and fever, including the deaths of any of them; and to report cases to the *thana* supervisor.

After each survey, 1500 villages were randomly selected to assess the efficacy of search. Assessment in Bangladesh was greatly facilitated by the fact that every house in the country was numbered—a practice begun by the staff of the malaria eradication programme and kept up by the smallpox eradication personnel. An assessment of the results of the April search revealed that surprisingly few villagers knew of the reward for reporting a case. On further investigation, it was found that health workers, wanting to claim the 50-*taka* reward for themselves, did not publicize it. This situation was corrected in May, when the reward was offered both to the person who reported the outbreak and to the first health worker to confirm it. The April assessment showed that only 30% of villagers knew of the reward, but by September this proportion had increased to 70%.

In contrast to the experience in India, the number of outbreaks discovered during each search was not high (Fig. 16.15). However, in India, the reward was not offered until many searches had been conducted, while in Bangladesh its existence was announced even before the first searches began. The searches in Bangladesh were more effective in increasing public awareness of the reward and in stimulating reporting than in detecting outbreaks. As an illustration, a review of the last 119 outbreaks which occurred showed that 55 (46%) had been detected by reports from the

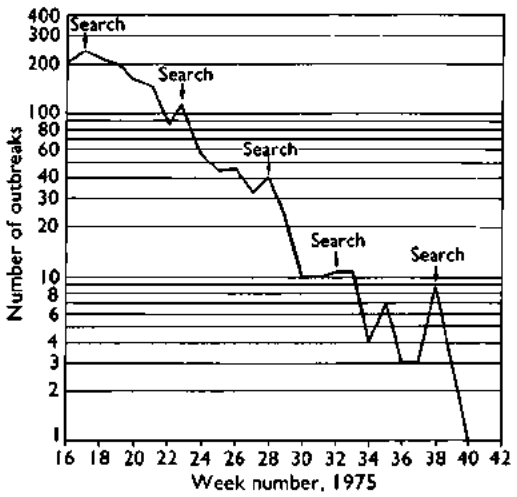


Fig. 16.15. Bangladesh: number of outbreaks detected by week, 1975.

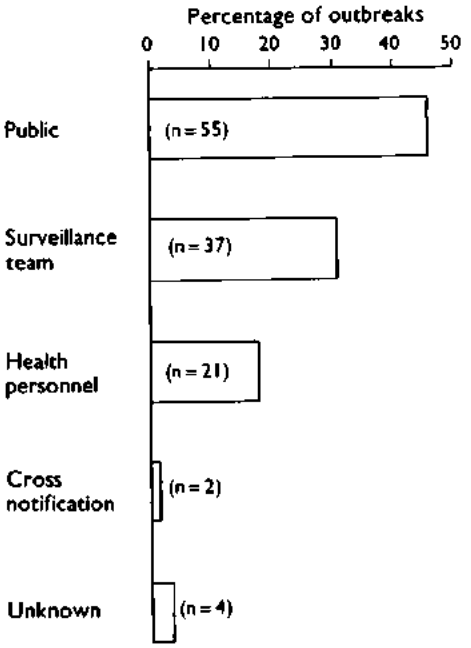


Fig. 16.16. Bangladesh: source of report of the last 119 outbreaks of smallpox.

public and 37 (31%) by surveillance teams (Fig. 16.16).

The number of personnel engaged in the programme was far larger than it had ever been. An estimate during the 3-month period of greatest activity revealed that an average of almost 12 000 persons were working each day (Table 16.16).

Between February and April, the number of reported cases steadily increased, from 1703 in February to 2467 in March and to 3948 in April. Smallpox appeared to be as great a problem in 1975 as it had been in 1974 although, on the basis of later surveys, it was estimated that 83% of all cases were reported in 1975 compared with only 49% in 1974 (Hughes et al., 1980).

The occurrence of epidemic smallpox extending throughout Bangladesh for a fourth year was politically uncomfortable for the Secretary of Health, a former surgeon. He fully accepted the idea of mass vaccination but was uneasy about the concept of a programme for detecting cases and containing outbreaks. The success of surveillance–containment operations in 1970 did not convince him. His personal experience with smallpox control in the Ministry had been confined to the period since Bangladesh's independence, and for the last 4 years optimism had been expressed by the staff during and immediately after the monsoon each year, but epidemics and emergency programmes inevitably followed in the spring. For advice he turned most often to the WHO Representative in Bangladesh, a public health physician but one who understood neither smallpox epidemiology nor the eradi-

Table 16.16. Bangladesh: personnel employed during the 3-month period of maximum containment of the smallpox eradication programme, May–July 1975

Personnel category	Number	Number of days per man per 3 months	Total number of man-days in 3 months[a]
Headquarters staff	80	75	6 000
Epidemiologists	90	80	7 200
Area and *thana* surveillance officers	500	30	15 000
Surveillance team members	400	75	30 000
Health staff for 2 searches	12 000	12	144 000
Containment:			
Health staff	1 000	70	70 000
Emergency field workers	10 000	90	900 000
Total	24 070	–	1 072 200

[a] The number of man-days per month totalled 357 400, or an average of 11 913 persons working every day.

cation strategy any better than the Secretary of Health. With smallpox incidence rising and with increasing international interest as to whether Bangladesh could or would be able to stop transmission, tensions were great. The Secretary of Health and the WHO Representative repeatedly and vehemently demanded that the surveillance–containment programme should be stopped and the entire population vaccinated forthwith. Dr Mahboober Rahman and his national and WHO colleagues argued that mass vaccination was futile, that vaccinial immunity was already high and that the surveillance–containment approach offered the only possible solution. Indeed, the level of vaccinial immunity, as shown in a 1976 national survey was 91% overall.

However, without notice to the programme staff, the Secretary of Health would periodically order the health staff in a district or subdivision to stop all other activities and to vaccinate everyone in the area concerned. Usually, this was accompanied by threats of punishment if any unvaccinated person was discovered at the end of 7 days or some such brief period. After lengthy discussions, the Secretary would eventually be persuaded to rescind the order, but, not infrequently, for many days outbreak containment programmes were abandoned and surveillance was stopped. Further problems occurred when the Secretary and the WHO Representative made one of their frequent visits to the field. The Secretary would announce that on his trip, he would stop at villages along his route and expect to find that every single person had been vaccinated. A flurry of activity ensued to vaccinate everyone along the route he was expected to follow, again at the expense of outbreak containment measures. An even more serious problem arose when he required senior staff to pledge to resign if cases of smallpox were found after a certain date, an action which resulted in the suppression of reports of cases. The problem was not finally resolved until April, when the WHO Representative returned to Geneva and was replaced by the able Dr Eung Soo Han. The Secretary's continuing concern about his and his country's image was reflected in May 1975 by his decision not to attend the World Health Assembly. Instead, he dispatched Dr Rahman to respond to the anxious inquiries he knew would be expressed about the Bangladesh smallpox eradication programme.

THE FINAL CHAPTER

From April to August, the number of infected villages decreased at a substantially more rapid rate than in preceding years—from 1280 in April to 131 in July. The staff began to chart weekly the number of "active cases" still present—i.e., the number of cases in which the scabs had not yet been shed. In a progress report to WHO staff in July 1975, Henderson wrote: "Some years ago . . . we had plotted progress on a country and provincial basis, subsequently on a district basis and then by blocks/*thanas*. In now monitoring the numbers of individuals capable of transmitting infection, I believe we've reached a final stage." The last case in India, the last of 32 importations from Bangladesh, occurred in May, leaving Bangladesh the only endemic area in the whole of Asia. The search in July detected 33 outbreaks and that in August only 7. With the extensive resources available and a programme functioning so well, the end once again appeared to be in sight. There was, however, one further tragic event.

On 15 August, Sheik Mujibur Rahman, the first President of Bangladesh, revered as the father of the country, was assassinated in a military coup. The airport was closed and the borders sealed. Communications by radio were suspended for 2 weeks and although field staff continued to work, movement in and out of Dhaka was limited. Fearing that vehicles might be seized, the smallpox eradication staff hurriedly dispersed them from the motor pool to locations all over the area. For nearly a month, most of the staff remained apprehensive that civil war might again occur and, with it, the movement of hundreds of thousands of refugees—and renewed epidemics of smallpox. India, meanwhile, greatly strengthened its complement of staff in border areas. Fortunately, the country remained quiet, the monsoon rains were plentiful, an excellent crop was harvested and the enormous movement of refugees ceased.

The post-monsoon period was not, however, without incident, as a Japanese scientific team arrived in Dhaka bringing with them a new laboratory technique for the rapid diagnosis of smallpox. It was a propitious moment at which to undertake the investigations, since Dr Farida Huq, a highly competent virologist, was present in Dhaka at that time and able to perform confirmatory studies on specimens from suspected cases. The new immunofluorescence technique seemed capa-

Plate 16.13. Smallpox eradication programme offices in the field were simple but functional like this one in Chandpur *Thana*.

ble of identifying variola virus in pus or scabs within hours (instead of days) after a specimen had been submitted. Only 19 villages were infected in September as the team began its work, but many of the first specimens examined were reported as positive for variola virus. Surveillance teams were then taking many specimens from cases which they had diagnosed as chickenpox, simply to confirm by laboratory test that smallpox was not present. Many of these specimens were reported to contain variola virus and for weeks consternation and bewilderment prevailed as containment operations were begun and then stopped in numerous presumed outbreaks. There was a strong suspicion that something had gone seriously awry when immunofluorescence staining showed that material taken from a boil on the back of one of the WHO advisers contained variola virus. A technique which had worked well in the laboratory had failed when used in the field, and was soon stopped (Tarantola et al., 1981).

THE LAST OUTBREAK

When the conflicting laboratory and clinical data had been resolved, it became clear that smallpox transmission had apparently been terminated– the last known case having occurred on 14 September. Over the succeeding weeks, 8 previously undetected outbreaks were discovered in Patuakhali, Barisal and Dhaka but in none had cases occurred after 14 September. The monthly programmes of systematic search continued and, except in these three districts, independent assessement showed excellent results. At the beginning of November, civil disorder erupted, with local fighting breaking out in three different parts of the country. The United Nations was sufficiently concerned to recall its personnel to Dhaka. Only the WHO smallpox eradication staff remained in the field. But no additional cases could be found.

The progress of the smallpox campaign in Asia had been followed closely by the press, which believed, as did the personnel involved, that eradication of smallpox from Asia was the most formidable obstacle to global eradication. Early in November, 6 weeks after the onset of the last case, the only active outbreak in Asia was scheduled to be removed from the list. It was agreed, however, that caution was required and an additional 2 weeks should be allowed to elapse before an announcement was made. No cases occurred, and on 14

November 1975 WHO announced at a press conference that 2 months had passed since the onset of the last case in Bangladesh; and while the intensive search for cases would continue in Bangladesh and other countries, there was at that time no known patient in the whole of Asia, indeed in the world, with variola major. On the following day, 15 November, the eradication programme's telex control room received the following cable from the densely populated Bhola Island, off the southern coast:

"ONE SUSPECT SMALLPOX CASE DETECTED VILLAGE KURALIA [UNION COUNCIL] SOUTH DINGALDI [POLICE STATION] BHOLA DATE OF DETECTION 14/11/75 DATE ATTACK 30/10/75 CONTAINMENT STARTED DETAILS FOLLOW".

(The date of onset was later confirmed to be 16 October 1975.)

A team of epidemiologists immediately left Dhaka for Bhola Island expecting to find a misdiagnosed case of chickenpox. They reached the infected house only after a 24-hour journey by speedboat, steamer, Jeep, motor cycle and finally on foot. The diagnosis was not in doubt: it was smallpox, and this was confirmed days later by the laboratory. Everyone was concerned. It was November, the monsoon was over, and the season when smallpox was most rapidly transmitted was at hand. If there was one case, there had to be others in the chain of transmission.

Bhola Island, located at the mouth of the Ganges, had a population of 960 000 and an area of approximately 2600 square kilometres. Regular ferries connected the island with the mainland and other islands and these were heavily used.

In 1970, Bhola had been devastated by a tidal wave, which was followed by a relief operation that included a smallpox vaccination campaign. Because of this, the proportion of persons with a vaccination scar was higher than in most of the country. During 1974 and 1975, few smallpox cases had been reported. However, in August 1975, it was discovered that a medical officer had failed to report known outbreaks. Subsequently, surveillance had been reinforced, and since the beginning of August 141 cases and 33 deaths had been detected. All but 2 of the outbreaks, one of 43 cases and one of 44, had ceased before discovery. Once again, investigation revealed the suppression of reports and so, early in October, an additional surveillance team had been sent from another area, the Bhola surveillance team reorganized, and an epidemiologist posted to the island for full-time work.

On 6 November 1975, while conducting a search of markets, the Bhola surveillance team received information about an outbreak in Kathali village. During the course of investigating and tracing the sources of infection, the team discovered outbreaks in 3 other villages with cases extending back to 2 March. A search began within a 5-mile (8-kilometre) radius of each of these villages. During a tea break in one of the markets, the surveillance team obtained information about the death of a person with rash in the village of West Joynagar, 5 kilometres to the south.

The death had been reported to the *thana* smallpox eradication officer, who had sent a family welfare worker to investigate. His conclusion had been that the death was caused by measles. On investigation, the surveillance team was in no doubt that it was due to smallpox. A search revealed an outbreak of 7 cases and 3 deaths. One of the patients was a heavily pockmarked 8-year-old girl who informed the team that there were other cases in Kuralia village, some 200 metres to the west of her house. Investigation there revealed 2 cases, one of which was in a 10-year-old boy whose onset of illness was on 6 October and the other in a 3-year-old girl, Rahima Banu, who had become ill on 16 October.

By the time of investigation, Rahima Banu was the only known patient with active smallpox in all of Asia. Accordingly, extraordinary efforts were begun immediately to contain the outbreak and to discover other possible cases. The surveillance team which had detected the outbreak was soon joined by teams of epidemiologists from Dhaka and other areas. A launch brought vaccine, light transport (motor cycles and bicycles), speedboat engines, drums of petrol, kerosene lanterns, loudspeakers and other equipment. The patient, who still had a few scabs on her legs, was isolated at home. House guards were posted 24 hours a day; food and money were supplied to the family so that no one would have to leave the house. Vaccination of the 18 150 people living within a radius of $1\frac{1}{2}$ miles (2.4 kilometres) of the infected house was begun immediately. This task included day and night house-to-house vaccination, the enumeration of every household member, the checking of vaccination results, and the vaccination or revaccination of any newcomers to the village.

WHO / D. J. M. TARANTOLA

Plate 16.14. Rahima Banu, a 3-year-old girl from Bhola Island, Bangladesh, was the last case of smallpox in Asia and the last naturally occurring case in the world of variola major, the more virulent form of the disease. Her illness began on 16 October 1975, approximately 3 weeks before this picture was taken. The depigmented areas of her skin are sites where lesions were present.

The area within a 5-mile (8-kilometre) radius of the infected house was searched repeatedly by successive teams; each team searched for cases with fever and assessed the performance of the preceding team. The 7 markets and 9 schools, as well as all healers in the area, were visited repeatedly to pick up rumours of other cases. Each house on Bhola Island was searched by health staff under the guidance of epidemiologists and surveillance teams, which had been allocated specific geographical areas. This search also covered all public meeting-places such as markets, schools and tea-shops. Whenever it was reported that a member of any household in the outbreak area had left, the responsible authorities were notified so that the person concerned could be found, vaccinated and kept under surveillance.

A difficult problem was the poor means of access from the centre of the island to the shore, where most of the outlying villages could be reached only after a difficult journey by bicycle or on foot. Frequently, the paths leading to these villages were cut by small rivers caused by fluctuating tides. The settlements along the shore were occupied by landless peasants or fishermen, who were the most distant from health centres and the least likely to be visited by health staff. They were generally much less well vaccinated than other groups and unlikely to report any cases of smallpox. Accordingly, a dispensary-launch began a methodical village-by-village search, which had to be planned daily according to the tides. Local launches were used also.

A 500-*taka* (US$33.00) reward was offered to anyone reporting a case of smallpox. This was widely publicized through the use of posters, pamphlets, handbills, loudspeakers and, from Dhaka, the press and other media. Check-points were established at such places as bus stations, ferry docks and crossroads, where travellers converged. Information was collected about cases with rash and these were checked by mobile teams.

About 10 kilometres north of the site of the outbreak, in Bhola town, a control room was established where progress could be recorded on maps and charts. Radio communication was established to permit regular contact between the control room, the dispensary-launch travelling along the shore areas, and Dhaka.

The health staff engaged in this outbreak alone (within a 5-mile radius) consisted of 3 epidemiologists and more than 40 health staff and temporary workers. For the rest of the island there were 3 epidemiologists, and 180 specially deputed health workers to assist the subdivisional staff in the house-to-house searches. In addition, 16 emergency field workers worked at check-points and conducted municipal searches.

By 19 November, the fifth day after the discovery of the outbreak, the first round of vaccinations within the 1½-mile radius of the infected house had been completed. A second round was begun, covering the same area, and was completed 8 days later. Of a listed population of 18 150, 16 295 were vaccinated. A later assessment showed that 100% of the residents living within a half-mile radius and 95% of those living within a 1½-mile radius of the infected house had been vaccinated.

WHO / P. ROBERTS, 1975

Plate 16.15. Mohammed Matiur Rahman (b. 1932), a medical officer with the national programme in Bangladesh, questioning villagers about possible smallpox cases during the search on Bhola Island.

Meanwhile, 2 consecutive house-to-house searches within the 5-mile radius were completed by 8 December. Among the 120 000 population, 52 individuals with fever and rash were found, including 17 with chickenpox and 11 with measles, but there were no cases of smallpox. During the following 2 months, 2 additional house-to-house searches of Bhola Island were conducted. During these operations, 2 more unreported smallpox outbreaks were discovered: one had occurred in 1974 and had resulted in 18 cases and 6 deaths; the second involved 1 person, who had become ill in July 1975.

At the end of December, the additional staff who had been sent to Bhola began to be recalled to their respective districts. Kuralia was declared smallpox-free and the 2-year post-epidemic surveillance period commenced.

MORBIDITY AND MORTALITY DATA

To obtain precise data on the age distribution and case-fatality rates for smallpox, special studies were undertaken in 1976 to enumerate all cases and deaths in 165 outbreaks, including 115 that constituted the last outbreaks in the country, and 46 others, which were investigated in northern Bogra District. In all, 1127 cases were recorded (Table 16.17).

Cases occurred among all age groups but the youngest were the most heavily afflicted. Of the total, 55% occurred among children under 10 years of age, a group that made up only 34% of the population. Overall, the case-fatality rate was 18%, comparable to that in India. The much higher case-fatality rate among males over 20 years than among females in the same age group was notable but no explanation was found for this disparity.

CONCLUSIONS

The programme in Bangladesh was uniquely distinguished by extremes—with peaks of optimism and success alternating with catastrophic setbacks resulting from natural disasters of flood and famine and man-made disasters inflicted by civil war and the disruptive reorganization of the health services. The frustration and pessimism of the programme staff during the spring of 1975 were matched only by the feelings of their counterparts in Bihar State, India, 6 months earlier and are vividly depicted in the book *Quest for the Killers* (Goodfield, 1985).

The successful application of a surveillance–containment programme in the spring of 1970 had so rapidly and so easily interrupted transmission that it was difficult to believe that the success could not be repeated in 1972 or in the 2 succeeding years. In retrospect, the 1970 experience in Bangladesh to some extent paralleled events in India, where, for example, transmission was so rapidly interrupted in Tamil Nadu State (population, 41 million) in 1968 and in Gujarat State (population, 27 million) in 1971. These successful programmes engendered unwarranted confidence that transmission could be quickly interrupted in a population already reasonably well vaccinated and with so numerous a health staff available. What was not appreciated was the dearth of supervision of the host of health workers in many parts of India and in Bangladesh. Given optimum conditions of population stability, vigorous and enlightened senior programme leadership and the application of surveillance–containment

Table 16.17. Bangladesh: cases of and deaths from smallpox and case-fatality rates in 165 outbreaks, by age and sex, 1975

Age group (years)	Males			Females			Total		
	Number of cases	Number of deaths	Case-fatality rate (%)	Number of cases	Number of deaths	Case-fatality rate (%)	Number of cases	Number of deaths	Case-fatality rate (%)
0–4	148	35	24	188	55	29	336	90	27
5–9	128	17	13	151	23	15	279	40	14
10–19	101	17	17	95	14	15	196	31	16
⩾20	154	34	22	162	14	9	316	48	15
Total	531	103	19	596	106	18	1 127	209	18

measures at a declining or low point in the long-term periodicity of smallpox, a modest surveillance–containment programme was rapidly and dramatically successful. When natural or man-made disasters created hordes of refugees, when leadership was deficient or when smallpox was at the height of its periodic wave, it became apparent that the health structure had little in reserve with which to cope with the situation.

Progress in programmes in the northern and eastern states of India had been disappointing and frustrating, but within little more than a year after the special intensified national programme began in September 1973, transmission was interrupted. In Bangladesh, however, the interruption of transmission, once successfully achieved, was frustrated in each of 3 successive years by unexpected disasters. With courageous confidence, bolstered by material support from Sweden and other countries, a remarkably diverse national and international staff made one more heroic effort in 1975 and succeeded in attaining their goal. If civil war had broken out in August 1975, following the assassination of Sheik Mujibur Rahman, transmission would probably have persisted for at least another year and might perhaps still be occurring. History records, however, that Rahima Banu was the last victim of variola major—on 16 October 1975.

CHAPTER 17

WESTERN AND CENTRAL AFRICA

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INTRODUCTION

Progress in smallpox eradication throughout most of Africa was more rapid than in Asia, despite the fact that the majority of African countries had less developed health service infrastructures, poorer roads and communications and proportionately fewer health personnel. The rapidity with which smallpox was eliminated in an area embracing 21 countries of western and central Africa (Fig. 17.1) was especially significant. Programmes in all but one of the countries in this region were supported by the United States Agency for International Development (AID) with technical direction and coordination provided by the United States Communicable Disease Center (CDC), later called the Centers for Disease Control. Most national programmes in this area began early in 1967 and all were fully operational by January 1968. By September 1969, every country except Nigeria had interrupted smallpox transmission, and in May 1970, only 3½ years after field operations had begun, the last case in this region was detected. Within this brief span of time, smallpox had been eliminated from some of the least developed and most

heavily infected countries in the world—from a contiguous area greater in size than the continental USA, inhabited by 111 million people (the estimated population in 1967).

From November 1965, when the USA decided to support the smallpox eradication effort in western and central Africa, this programme played a pivotal role in the ultimate achievement of global eradication. The resolve of the USA to commit substantial resources lent encouragement to the Nineteenth World Health Assembly's decision in 1966 to embark on the Intensified Smallpox Eradication Programme. Programme staff made important early contributions to the development and improvement of field operations; their observations changed the understanding of the epidemiology of smallpox and served to alter the global strategy. The demonstration that smallpox could be eliminated rapidly throughout such a vast developing area provided a crucial impetus to programmes in other countries and convincingly showed that the goal of eradication was realistic, even in areas in which health services were the least adequate and in which difficult problems—even civil war—had to be surmounted. Finally, many individuals who acquired experience in this regional programme subsequently made important contributions to the development and execution of programmes in other parts of the world.

The activities and decisions leading to the development of this endeavour are thus of particular significance. Interestingly, despite the importance of the programme, the USA's decision to contribute to it did not result from a considered policy judgement to support the WHO Intensified Programme as such. Rather, it began as an ancillary objective in a multicountry programme for the control of measles in many of the less populous countries of this region.

After the programme had begun, the staff of CDC bore full responsibility for its technical guidance and coordination, although they

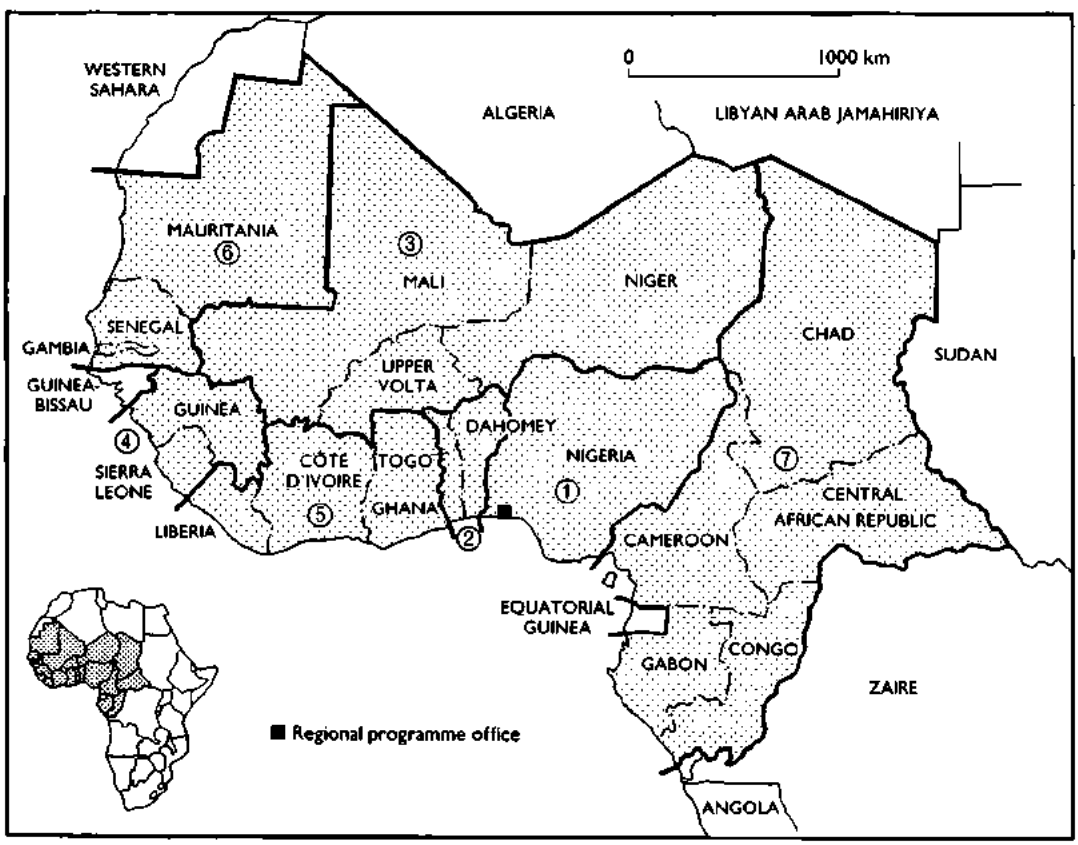


Fig. 17.1. Western and central Africa: countries that participated in the smallpox eradication and measles control programme, 1967–1972. The bold lines and circled numerals indicate the country groupings under which the national programmes are discussed in the text.

Changes in Political Status and Names of Countries

In 1967, when the AID-supported regional programme began, all but 2 of the 21 countries (Equatorial Guinea and Guinea-Bissau) shown in Fig. 17.1 were independent States. Liberia had enjoyed sovereignty since 1847 but 18 others had become independent between 1957 and 1965. Thirteen had been colonies of France and were commonly referred to as francophone countries. These were the Central African Republic, Chad, the Congo, Côte d'Ivoire, Dahomey, Gabon, Guinea, Mali, Mauritania, Niger, Senegal, Togo and Upper Volta. Cameroon, which had been administered jointly by France and the United Kingdom, was officially bilingual. Four—namely, the Gambia, Ghana, Nigeria and Sierra Leone—had recently obtained independence from the United Kingdom.

Equatorial Guinea (population in 1967, 278 000), a colony of Spain, became independent in 1968 and subsequently received supplies and equipment from the USA for smallpox and measles vaccination. Guinea-Bissau (population in 1967, 525 000), a colony of Portugal, became independent in 1974 after assistance from the USA to the regional programme had terminated.

Two countries changed their names after the programme's conclusion. Dahomey was renamed Benin in 1975, and Upper Volta was renamed Burkina Faso in 1984. In this chapter, which describes activities before 1975, the former names, Dahomey and Upper Volta, are used.

kept in close contact with WHO staff responsible for the global programme. WHO's contributions were modest, consisting mainly in the provision of bifurcated needles, an average annual subvention of US$200 000 to cover local costs, technical support to one programme (Mauritania) and the organization of activities pertaining to the certification of eradication in 1976. The remarkable achievements in this part of Africa are therefore primarily those of the national governments and staff, AID and the personnel of CDC.

THE REGION OF WESTERN AND CENTRAL AFRICA

Within the region defined in this book as western and central Africa were 21 countries, of which 14 reported cases of smallpox in 1966 (Table 17.1). The predominant form of smallpox was variola major with a case-fatality rate of 5–15%. Because established health services were few and reporting was very incomplete, the actual geographical extent of smallpox and its true incidence were uncertain when the programme began.

The region was diverse both in ecology and in culture. Rain forests predominated along the coast, giving way to savanna and finally to the Sahara desert. Throughout the region, hundreds of tribal groups speaking their own local language were organized into various tribal and theocratic societies which often transcended national boundaries. Road systems were generally poor, communications were difficult, and newly created governments were only beginning to cope with the array of problems associated with the development of education, agriculture, industrialization and health services. Smallpox was but one of many problems for which resources were few and trained manpower was limited.

CDC and WHO staff were in agreement that if smallpox could be eliminated from this entire region, importations would be infrequent and their containment would probably not present a serious problem. To the north lay the Sahara desert and the smallpox-free countries of Morocco, Algeria and Libya and the Spanish province of Western Sahara. To the east was the Sudan, then free of smallpox. To the south-east of the region was the Democratic Republic of the Congo (later renamed Zaire), the only adjacent country infected with smallpox. It bordered on the Central African Republic and the Congo. The latter two countries, in 1966, were thought to be smallpox-free and there were few travellers

Table 17.1. Western and Central Africa: number of reported cases of smallpox, by country, 1961–1970

Country	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970
Cameroon	1 145	743	135	88	28	2	119	37	3	0
Central African Republic	0	57	3	0	0	0	0	0	0	0
Chad	502	769	10	5	73	0	86	5	0	0
Congo	23	1 254	1 476	198	89	0	0	0	0	0
Côte d'Ivoire	4 656	2 141	282	623	27	10	2	0	0	0
Dahomey	119	132	249	703	168	490	815	367	58	0
Equatorial Guinea	0	0	0	0	0	0	0	0	0	0
Gabon	0	1	111	49	1	0	0	0	0	0
Gambia	12	4	52	6	6	3	0	0	0	0
Ghana	70	145	23	9	7	13	114	24	0	0
Guinea	96	2 948	224	320	70	56	1 530	330	16	0
Guinea-Bissau	0	7	0	0	0	0	0	0	0	0
Liberia	1 116	325	88	258	40	32	6	5	0	0
Mali	1 706	1 521	1 096	343	626	281	293	134	1	0
Mauritania	12	40	0	0	2	76	0	0	0	0
Niger	1 740	1 038	445	330	463	1 023	1 187	678	28	0
Nigeria	3 600	3 864	1 778	1 430	4 566	4 953	4 753	1 832	203	66
Senegal	201	232	231	2	2	0	0	0	0	0
Sierra Leone	6	78	14	90	60	293	1 697	1 143	80	0
Togo	281	571	285	34	13	201	332	784	83	0
Upper Volta	2 360	1 550	341	8	14	69	195	100	0	0

from the Democratic Republic of the Congo into either of them because of the difficult terrain and political restrictions on travel.

In countries which had formerly been colonies of the United Kingdom, health care was provided primarily through government or mission health centres or dispensaries, some of which performed smallpox vaccination using glycerolated or lanolinated vaccine produced in Nigeria or the United Kingdom, although many offered no immunizations whatsoever. Mobile health units periodically augmented the vaccination effort in Ghana and in parts of Sierra Leone and southern Nigeria. The control of smallpox outbreaks was the delegated responsibility of district or local medical officers and, in some instances, mobile medical field units. As in other countries, the health personnel responded with varying degrees of interest, but even where efforts were made to control smallpox, these were frequently unsuccessful because of the use of the heat-labile, sometimes low-potency vaccine. Of the countries relying on this approach, only Ghana and the Gambia had succeeded in achieving a substantial measure of smallpox control. Ghana's success could be attributed to its mobile medical field units and to health inspectors who took special care in preserving the thermolabile vaccine and who diligently investigated and contained reported outbreaks by vaccination. The Gambia, too small in area and population to permit long-sustained transmission of smallpox on its own, was partially insulated from importations by the surrounding, comparatively well vaccinated population of Senegal. Liberia, in which a mass vaccination campaign with freeze-dried vaccine had been conducted in 1962, followed by a WHO-supported programme, reported few cases. In northern Nigeria and Sierra Leone, however, vaccinial immunity in 1967 was especially low and smallpox was a serious problem.

In the former French colonies, disease control was primarily the responsibility of multi-purpose mobile teams of the local endemic diseases control service (Service des Grandes Endémies), which systematically moved throughout the country endeavouring to reach each village once every 2–3 years (Richet, 1965; Labusquière, 1967). Government health centres and dispensaries also existed but were less numerous and generally less well supported than in the former British colonies; mission hospitals and health centres were few. The multi-purpose teams administered smallpox vaccine and undertook other preventive measures, such as those aimed at controlling yellow fever, trypanosomiasis, yaws and leprosy. In most of the countries, a French-produced, freeze-dried vaccine had been used since the early 1920s (Fasquelle & Fasquelle, 1971). The degree of potency and stability of this vaccine is unknown, but when freeze-dried smallpox vaccine of reasonably high titre began to be used extensively in the early 1960s, and in areas in which the multi-purpose teams continued to function, smallpox incidence declined rapidly; in some countries, the disease had disappeared by

Plate 17.1. Villagers in Côte d'Ivoire line up for smallpox vaccination during the campaign that eliminated smallpox from that country in 1966.

1967. Thus, the numbers of reported cases in 1966 were few or nil throughout the former area of French Equatorial Africa (Cameroon, Central African Republic, Chad, the Congo and Gabon), as well as in Mauritania, Senegal and Upper Volta. In Mali, a WHO-supported programme begun in the early 1960s had markedly reduced smallpox incidence, and in Côte d'Ivoire specially constituted mobile smallpox vaccination teams interrupted transmission in 1966. In the other francophone countries, multi-purpose teams functioned less effectively, and in some of them had ceased to function altogether; in Dahomey, Guinea, Niger and Togo, smallpox continued to be an important problem.

ORIGINS OF THE REGIONAL PROGRAMME, 1961–1965

The decision by the USA in November 1965 to support a region-wide programme of smallpox eradication and measles control had its origin in a small-scale field trial of the newly developed Edmonston strain measles vaccine, which was conducted in 1961 in Upper Volta (Meyer et al., 1964a). This vaccine had been found to be safe and effective when given to children in the USA but because it frequently induced high fever, gamma-globulin was given simultaneously to diminish symptoms. Under the difficult field conditions in developing countries, the administration of both the measles vaccine and gamma-globulin was not feasible. Both had to be given subcutaneously, and while a jet injector could be used to administer measles vaccine, a needle with syringe was required for the more viscous gamma-globulin. Expense was another factor, the vaccine and gamma-globulin costing nearly US$2.00 per dose. Most developing countries could not afford to spend scarce foreign exchange on vaccines costing even a small fraction of this amount.

In 1960, Dr Paul Lambin, Minister of Health of the newly independent country of Upper Volta, was told of the new vaccine while visiting the United States National Institutes of Health (NIH). Because of the severity of measles in African children (Morley, 1962; Cantrelle, 1965), the vaccine was of special interest to him. Accordingly, he proposed that a study should be undertaken in Upper Volta to determine whether the

WHO / P. N. SHARMA, 1961

Plate 17.2. Paul Lambin, Minister of Health of Upper Volta (Burkina Faso), obtained support from the USA in 1961 for a national measles vaccination campaign. This was followed by similar campaigns in other francophone countries of western Africa and, eventually, by the smallpox eradication and measles control programme assisted by AID in 20 countries of western and central Africa.

measles vaccine without gamma-globulin could be given safely to African children. Concern about its safety was legitimate, since it was feared that the high fever it induced might prove harmful or even fatal to children suffering from such conditions as tuberculosis or malnutrition.

With support from NIH, Dr Harry Meyer and his colleagues studied a group of 600 children in Upper Volta in 1961 (Meyer et al., 1964a). They demonstrated that the vaccine without gamma-globulin could be administered with safety and efficacy. Dr Lambin was impressed by the results and requested the USA to provide support for measles vaccination for all young children throughout the country. This request was granted and between November 1962 and March 1963, the multi-purpose mobile teams of the endemic diseases control service in Upper Volta, assisted by Dr Meyer and his colleagues, vaccinated 731 548 children (Labusquière, 1967). The number of reported cases of measles declined sharply, and during the next 2 years remained well below previously recorded levels.

Information about this campaign was widely communicated by Upper Volta to other member countries of a regional health organization, the Organization for Coordination and Cooperation in the Control of Major Endemic Diseases in West Africa (Organisation de Coordination et de Coopération pour la Lutte contre les Grandes Endémies en Afrique de l'Ouest —OCCGE), whose headquarters were in Upper Volta. The organization comprised most countries of the former area of French West Africa (Côte d'Ivoire, Dahomey, Guinea (until 1965), Mali, Mauritania, Niger, Senegal and Upper Volta). At the request of OCCGE, AID agreed to support additional national campaigns, and thus it was arranged for Dr Meyer to conduct training and demonstration projects in 6 of the countries (Côte d'Ivoire, Dahomey, Guinea, Mali, Mauritania and Niger) late in 1963. During the following year, AID allocated US$1 478 000 for the provision of vehicles, jet injectors and measles vaccine to vaccinate 25% of the children between 6 months and 6 years of age. Towards the end of 1964, the measles vaccination campaigns began.

AID staff had assumed that the execution of the campaign would be comparatively straightforward, given the success in Upper Volta and the long experience of the multipurpose mobile teams in each of the countries. The fact that not all the endemic diseases control services were of the same quality as that in Upper Volta was not appreciated. The ensuing difficulties were compounded by the problem of introducing a new technology—the jet injector—which at that time required electric power and was difficult to repair and maintain, and a new vaccine, which had to be refrigerated until reconstituted for use. To conduct the mass measles vaccination campaigns, most countries curtailed or stopped the activities of the multi-purpose mobile teams because national resources were too limited to permit the two sets of activities to be continued.

With the beginning of the mass campaigns, it was decided that such technical assistance as might be needed from the USA should be provided by CDC, the agency primarily concerned with the field implementation of disease control programmes. Thus, in December 1964, Dr Lawrence Altman of CDC was requested by AID to spend 6 weeks in the countries to observe the campaigns and to report on progress. He found few of the campaigns to be progressing at all satisfactorily and eventually spent 6 months endeavouring to bring order out of chaos, albeit with little success.

Despite the difficulties, AID decided to offer assistance to an additional 4 countries (Cameroon, Central African Republic, Chad and Togo) to permit them to begin mass measles vaccination campaigns in 1965–1966. The potential scope of the project was even further expanded when, late in June 1965, the manufacturer of the measles vaccine brought the persuasive Dr Lambin to the USA on a special tour. The Director of AID was impressed with Dr Lambin and asked that a plan be drawn up for a comprehensive programme of assistance for measles vaccination in 16 African countries, including all the former French colonies of western and central Africa, as well as the Gambia, Liberia and Sierra Leone. Recognizing that this implied the need for more technical assistance staff than had been foreseen, AID asked CDC whether 9 epidemiologists could be made available in the autumn of 1965, each to serve on temporary duty for periods of 4–6 months in the countries in which campaigns were either in progress or due to begin.

The Addition of Smallpox Eradication as an Objective

Until July 1965, CDC personnel had not been involved in the development of policy or plans for the measles vaccination campaigns. However, if CDC were to provide so many epidemiologists for such extended periods of time, its own programmes would have to be curtailed or substantially altered. Accordingly, an examination of priorities and alternatives was undertaken, a responsibility assigned to Henderson, then Chief of the CDC Surveillance Section, from which most of the epidemiologists would be drawn.

To Henderson and his colleagues, the programme, as then conceived, did not represent sound public health policy. AID foresaw a 4-year programme during which each year all children from 6 months to 6 years of age would be vaccinated against measles in one-fourth of each country. At the conclusion of the programme, AID staff reasoned that all children would have been vaccinated and that the country would assume responsibility for continuing to vaccinate children who were born after the programme had terminated. It seemed unreasonable to CDC staff to assume that the impoverished African countries would be able to bear the recurring expenditures, given that measles vaccine then cost more than US$1.00 per dose; indeed, at that time, few of these countries could afford yellow fever vaccine, which was one-tenth as expensive. Had it been possible to eradicate measles from the area, vaccination conceivably could have been stopped, but this objective appeared unrealistic given the fact that no industrialized country, despite greater health resources, had yet eliminated the disease. At best, the reduction in measles incidence would be transient because almost all cases of measles in Africa occurred among young children and thus, within 3–4 years after vaccination in an area, measles incidence could be expected to approach levels comparable to those observed before the programme had begun. To embark on such a programme implicitly raised public expectations that the vaccine would continue to be made available as a routine preventive measure. If a government were to terminate its use abruptly after 4 years, possible repercussions from the public could be foreseen, particularly in the wake of the measles epidemics that would almost certainly follow.

In July 1965, however, the USA had already undertaken to provide assistance for measles vaccination campaigns in 11 western and central African countries; a proposal from CDC that no programme should be conducted was not acceptable. The combination of this programme with one designed to eradicate smallpox from the region appeared the most logical move, since it would provide an objective which offered hope of longer-term benefits. That the eradication of smallpox throughout a geographical region was feasible had been shown in other parts of the world. If this could be achieved, occasional cases might still be imported into the region and these would have to be contained. Smallpox eradication, however, seemed to be a more reasonable long-term goal than one which called for a continuing campaign of measles vaccination for all children. Moreover, as CDC staff reasoned, WHO and its Member countries were committed to a programme of global smallpox eradication and, although this was not progressing well, it was believed that a successful regional effort in one of the most highly endemic areas would represent an important contribution and perhaps a stimulus to other endemic countries.

Two other considerations—one technical and one political—also lent support to the idea of smallpox eradication. In 1965, CDC

had just completed a series of studies which demonstrated the efficacy and practicability of the intradermal administration of smallpox vaccine utilizing a newly developed nozzle for the jet injector (Millar et al., 1969; Neff et al., 1969; Roberto et al., 1969; Millar et al., 1971). The jet injector itself had been redesigned so that it could be powered by a pedal-operated hydraulic pump rather than by electricity; this offered a substantial advantage in field work. A second important consideration was the commitment made by the USA in 1965 at the Eighteenth World Health Assembly to provide support to the Intensified Smallpox Eradication Programme (see Chapter 9). Although the support then envisaged was for the development of a vaccine production laboratory in Kenya and assistance to smallpox eradication programmes in South America, it seemed reasonable to propose a broader initiative.

CDC therefore suggested that AID should support a region-wide programme of smallpox eradication in western and central Africa, with measles vaccination also being offered in countries selected by AID and where it was agreed by national authorities. This was a much bigger programme than that envisaged by AID, which had anticipated providing support to only 16 countries, with a total population of about 50 million in 1967. Two important countries in the region which were not then included—Nigeria and Ghana—together had a population of more than 60 million (see Table 17.9).

The proposal was strongly endorsed by officials of the United States Public Health Service—Dr Luther Terry, the Surgeon General, and Dr James Watt and Dr Benjamin Blood of the Office of International Health. AID readily accepted the proposal for a programme dealing with smallpox and measles in 16 of the countries but not for the inclusion of Ghana and Nigeria. As noted in an AID memorandum of 19 July 1965:

> "The total scope of the African problem is too great for any one donor to undertake its solution ... With a few exceptions [the 16 countries are among those] in which a modest demonstration of US interest and presence is desired without involving the USA in major dollar or personnel expenditures."

Despite these reservations, planning by CDC staff proceeded throughout the summer for an 18-country programme of 5 years' duration which would provide all supplies and equipment, plus a complement of CDC technical staff for work in individual countries, in an African regional office and at CDC headquarters in Atlanta. If accepted, this would be the first AID-supported technical assistance programme to be administered by CDC. On 20 August 1965, after many discussions between CDC and AID staff, the full proposal was formally submitted to AID. At the suggestion of CDC, Mr Milton P. Siegel, an Assistant Director-General of WHO, and Dr Karel Raška, Director of the Organization's Division of Communicable Diseases, visited Washington to discuss the proposal, and, early in November, the Director-General of WHO, Dr Marcolino Candau, also had meetings with AID and CDC staff. Everyone urged that the plan should be implemented, although a point at issue was whether WHO or perhaps another donor could support the programmes in Ghana and Nigeria. WHO officials stated that the Organization's resources were inadequate for the

BY COURTESY OF J. D. MILLAR, 1969

Plate 17.3. J. Donald Millar (b. 1934), a CDC epidemiologist, directed the AID-supported programme for smallpox eradication and measles control in western and central Africa from November 1966 to March 1970. As Chief of the CDC Smallpox Unit, he had supervised field studies of the jet injector and demonstrated its usefulness in large-scale programmes. He is holding a fetish statue of Sopona, a smallpox deity of some tribes of western Africa.

undertaking, and on the basis of WHO's experience with respect to voluntary contributions from national sources, little hope was offered that the necessary support could be found elsewhere.

AID was faced with a dilemma. Commitments had already been made for measles vaccination campaigns in 11 countries for which technical assistance was needed. It was difficult to find the requisite complement of technical staff at short notice except from the Public Health Service, but this the Public Health Service declined to provide unless all 18 countries were included in a programme that provided for smallpox eradication. The issue was settled, partly in response to a memorandum from the Public Health Service (see box), and the offer of assistance was formally announced on 23 November 1965. Thus began the first coordinated regional smallpox eradication programme.

GOVERNMENT AGREEMENTS AND ORGANIZATION OF THE PROGRAMME

The proposal for the regional programme envisaged that it would begin in January 1967, little more than 13 months after the decision had been made to offer assistance to the 18 countries. The schedule was optimistic, given the need to develop plans and obtain agreements with each of the countries, to recruit and train technical staff and to procure and deliver all the necessary supplies and equipment. Surprisingly, these goals were largely achieved, although not without problems.

Discussions in Africa began with the governments concerned immediately after the formal announcement. From 23 November to 17 December, a team composed of Henderson, Dr Clayton Curtis of AID, Dr Henry Gelfand of CDC and Dr Warren Winklestein, a CDC consultant, held meetings with health staff and discussed the programmes with officials of 16 of the 18 countries -at the ministerial meeting of OCCGE countries; at a technical meeting of a counterpart organization for former French colonies in central Africa, OCEAC, comprising Cameroon, Central African Republic, Chad, the Congo and Gabon (the Organisation de Coordination pour la Lutte contre les Endémies en Afrique centrale, or Organization for Coordination in the Control of Endemic Diseases in Central Africa); and in special visits to Guinea, Liberia, Nigeria, and Sierra Leone. Time constraints precluded visits by the team to the Gambia and Ghana, but government officials there communicated to the respective United States embassies their willingness to participate. Discussions were also held with staff of the WHO Regional Office for Africa attending the OCCGE and OCEAC meetings and by Henderson with the Director-General of WHO and his staff in Geneva.

The only one of the countries noted above for which assistance was not foreseen was the Congo, with which the USA then had no formal diplomatic relations. However, AID agreed to include the Congo, when confronted with the decision by OCEAC leadership that either all or none of its member countries would participate in the regional programme. With this addition, the number of countries increased to 19; when Equatorial Guinea became an independent country in 1968, it too, was included, bringing the number of countries assisted by AID to 20.

The national staff in each country enthusiastically welcomed the proposal for a programme of smallpox eradication and measles control, the latter being the principal attraction to countries in which smallpox was not a significant problem. The inclusion of Nigeria was vital to the success of the programme, since that country accounted in 1965 for nearly three-fourths of all reported smallpox cases and almost half the population of the region. It was most encouraging to learn that a senior health officer in the Nigerian Ministry of Health, Dr G. Adeyemi Ademola, had already elaborated a detailed plan for smallpox eradication which the government had approved and which he was about to dispatch to WHO and AID with a request for assistance.

During the visits in Africa, it became apparent that many United States officials assigned to the countries were not enthusiastic about the programme. As a matter of policy and personal conviction, they attached the highest priority to economic development programmes. Bilateral and multilateral assistance agencies generally considered at that time that improvements in health would follow naturally on economic development and that special programmes in the health sector would serve only to divert resources from the primary objective. Apart from this broader policy issue, the officials concerned anticipated that meeting what were termed

Memorandum of 10 November 1965
[Condensed from the original]

TO: Chief, Office of International Health
Through: Deputy Chief, Bureau of State Services
Acting Chief, Communicable Disease Center

FROM: Donald A. Henderson, M.D.
Henry M. Gelfand, M.D.

SUBJECT: Scope of the Proposed West African AID–CDC Vaccination Program

The principal scientific objectives of the West African vaccination program, as discussed in repeated meetings between ourselves and AID officials have been two: (1) the eradication of smallpox and (2) the control of measles as a significant health problem in the countries under consideration. Since our earliest meetings, it has been noted repeatedly that smallpox eradication was not a realizable goal unless conducted on a comprehensive regional basis.

We have sensed reluctance on the part of AID to include Nigeria and Ghana in the total scheme. The concept that WHO or the United Kingdom might wish to support the Nigerian program in concert with the AID effort in the other countries in this area has been propounded. From knowledge of WHO plans and programs, Dr Henderson can state categorically that it will be difficult for WHO to assign a high level of priority to a Nigerian project for the next few years. Whether the United Kingdom could and would undertake a Nigerian programme reasonably promptly and aggressively is a moot question. The probability that they would, however, is recognizably slight.

It must be reiterated that any multi-country West African smallpox *eradication* program in West Africa must from its inception include Nigeria in its development and planning. Short of so doing, the program is a *control* program only. As stated at the end of August in meetings with AID officials and Dr Karel Raška of WHO, the Communicable Disease Center does not feel that it is indicated nor does it wish to divert skilled personnel to assume full-time responsibility and direction of a program for smallpox and measles in West Africa limited to control only.

The problem of decision and timing with respect to this program is a second major consideration. To recruit capable medical staff ... commitments to them must be made in the fall of the year for employment beginning the following July. This has been firmly and clearly expressed in every meeting conducted with AID officials since early in the summer.

In the proposed program prepared in mid-August it was stated that, "It is important that this PASA [Participating Agency Service Agreement] be negotiated by mid-September 1965, in order that the USPHS may make the necessary staff commitments." We were later informed, however, that October 15 would be more realistic for a firm AID commitment. Postponement of the decision was again requested by AID to November 1 and then November 5. These dates have passed without decision.

In the meantime, a meeting of the Ministers of Health of the OCCGE countries has been scheduled for late November. It was felt by AID and PHS that Dr Henderson and Dr Gelfand should attend to initiate with the attending countries necessary discussions for programs next year. It was agreed, however, that such a trip would be essentially fruitless unless a commitment on the part of AID for full support to a West African program were forthcoming prior to the meeting. Since Dr Henderson and Dr Gelfand would have to depart about November 15, such a decision would have to be reached almost immediately.

Prospects of success for this program are already fading as a firm decision to undertake this activity is deferred. If decisions on the part of AID for full support to the 18-country program cannot be reached by November 15, the Public Health Service would be forced to withdraw such implied commitments as have been made and when AID decisions have been reached, discussions regarding the technical feasibilities would have to be re-explored from the beginning.

"local costs" would present insurmountable difficulties. During the visits of the CDC team the belief was repeatedly emphasized that most countries did not have adequate resources and that AID, as a matter of policy, did not provide for such local costs as the purchase of petrol and vehicle maintenance and repair. This policy had been adopted to ensure that, as far as possible, national governments would cover these recurrent costs by drawing on their own budgets, thereby fostering the continuity of programmes. For many governments, however, the resources available were so severely constrained that many fully equipped and fully staffed projects were unable to function for lack of comparatively small sums of money needed to buy petrol, for example. This potentially serious problem for the smallpox eradication–measles control programme was averted when the Director-General of WHO pledged to make WHO funds available to cover local costs when required. It was a decision about which he was politically uncomfortable since it meant that petrol purchased by WHO would be used to operate vehicles provided by the USA in a bilateral assistance programme. However, he abided by the commitment, and such support was eventually provided to 13 of the countries.

CDC staff had hoped that the overall regional programme could be phased in during a period of 2 years, some countries beginning operations in 1967 but as many as possible delaying them until 1968 to permit the necessary planning. For various reasons, however, such a delay was possible only in Guinea, Liberia and Sierra Leone. A programme in Nigeria was essential from the beginning of the regional effort, because of the size of the country and the fact that its central location made it the most logical site for the programme's regional office. Programmes had also perforce to be introduced in 1967 in the OCCGE and OCEAC countries because of commitments already made by AID for measles vaccination campaigns. Because of these and other political considerations, it was decided that programmes would have to begin in 1967 in 16 countries and in 1968 in the other 3.

The direction of the regional programme at CDC was yet another problem. A Smallpox Unit had been created in the CDC Surveillance Section in 1962 which, under the direction of Dr J. Donald Millar, had ably conducted studies on the use of the jet injector for smallpox vaccination and on the frequency of complications following vaccination. It was logical that he should assume direction of the regional programme but, in August 1965, he departed for a year's postgraduate study. In December 1965, with Dr Millar temporarily absent and no other suitable leadership available, Henderson relinquished his post as chief of the Surveillance Section to assume direction of the programme until Dr Millar returned. He was joined by his deputy, Mr Leo Morris, as well as by Dr Bernard Challenor, Dr Gelfand and Dr Ralph Henderson, and an administrative officer, Mr Billy Griggs—all CDC staff.

Within a month of the initial discussions with African health leaders, a 60-page document had been prepared which specified objectives and activities and identified needs and costs for personnel and commodities by country (Table 17.2). With minor modifications, this compilation was accepted by AID. The total cost of United States assistance was estimated to average about US$7 million per annum, of which approximately 40% was associated with the measles vaccination component, including storage refrigerators and jet injectors. It was anticipated that, on average, an additional US$1.7 million would be needed annually from WHO for local costs, a figure which, if correct, would have required 70% of all the WHO regular budget funds subsequently appropriated for smallpox eradication. Fortunately, the countries themselves eventually bore most of these local costs—WHO providing US$1.1 million to 13 countries from 1967 to 1972, or about US$200 000 per annum.

The projected size of the staff in the programme's regional office in Lagos and the central office in Atlanta, comprising about one-third of the total personnel, requires comment, as it was considered by some to be excessive and was accepted only with reluctance. The requirements, as outlined, arose from observations of other field programmes by CDC staff. It was believed that such programmes had regularly underestimated the need for central support and, indeed, this proved to be WHO's experience in establishing the Intensified Smallpox Eradication Programme. The regional office in Lagos was expected to exercise broadly delegated responsibilities for administration and field supervision. The personnel concerned were expected to travel extensively to effect coordination and to provide short-term emergency technical support, as well as to assist the Lagos

Table 17.2. Estimate of needs for western and central African programme[a]

Item	1967	1968	1969	1970	1971	Total
Supplies and equipment						
Doses of measles vaccine (thousands)	5 404	8 416	8 520	5 845	5 485	33 670
Doses of smallpox vaccine (thousands)	26 781	43 691	45 626	19 571	16 691	152 360
Vehicles	111	82	117	41	108	459
Vehicle spare parts (units)	144	220	218	178	167	927
Jet injectors	207	364	376	205	187	1 339
Refrigerators	126	81	118	38	108	471
Field equipment (units)	120	77	112	36	103	448
Boats	10	0	0	10	0	20
Professional personnel						
Field staff:						
Medical officers	14	18	18	17	12	—
Operations officers	16	23	23	23	23	—
Regional office staff	8	8	8	8	8	—
CDC office staff	8	8	8	8	8	—
Total	48	57	57	56	51	—
Total AID support costs (thousands of US$)	6 653	8 488	8 845	6 282	6 179	36 447
Local costs (thousands of US$)[b]	1 404	2 523	2 629	1 012	829	8 397

[a] From a document prepared by CDC, 21 January 1966; estimates did not include requirements for the Congo.
[b] Expected to be met mainly by WHO.

laboratory in the development of vaccine production. The document proposed the recruitment of 2 medical officers, 2 administrative officers, an equipment specialist, a health educator and a virologist. The CDC staff in Atlanta would be responsible for liaison with AID staff in Washington and with other agencies, for the recruitment and training of staff, for the development of instructional manuals, for the procurement and shipment of supplies and equipment, for the provision of longer-term emergency assistance in problem areas, and for the conduct of special studies pertaining to the programme. Although practical realities eventually required a redefinition of the respective roles of the two offices, experience demonstrated that the proportionately large staff in the central and regional offices, and the flexibility in assigning personnel which this implied, were vital to the rapid progress ultimately achieved.

In the programme document, the primary goal was specifically stated to be the eradication of smallpox, with measles control as a secondary objective, but longer-term objectives were envisaged:

"1. The establishment or, in some countries, improvement of mobile disease control services capable of administering vaccines or other preventive medications efficiently, economically and on a mass scale throughout the country.

"2. The establishment in each country of a system of disease surveillance broadly applicable to a variety of communicable disease problems.

"3. The development of highly simplified statistical sampling techniques applicable in these developing countries which will permit rapid assessment of disease problems.

"4. The establishment of elementary virological laboratories ... for the diagnosis of smallpox. [This objective was soon abandoned, as it was in other areas, when it became clear that the clinical diagnosis of smallpox was usually sufficiently accurate for surveillance purposes, and when it was discovered that laboratory diagnosis by the more sophisticated electron microscopy offered substantial advantages over traditional methods.]

"5. Improvement of the existing smallpox vaccine production laboratory in Nigeria such that it [can produce] vaccine of the multiple puncture type in quantities sufficient for Nigeria and other countries in the area."

PREPARATION FOR THE CAMPAIGN, JANUARY–DECEMBER 1966

As might be expected in the development of a new programme of this magnitude, the preparatory phase, during January–December 1966, was characterized by hectic activity and administrative frustration. A director for the CDC regional office to be established in Lagos, Dr George Lythcott, was recruited early in 1966. He, with Dr Gelfand and Dr Ralph Henderson, travelled throughout western and central Africa drawing up pro-

gramme agreements for each country. Such agreements, however, could not be formally signed nor could the procurement of supplies and equipment begin until the United States Congress had passed the act which appropriated the funds. Although this had been expected before 1 July, when the government's fiscal year began, the Foreign Assistance Act of 1966 was not signed until 19 September. The difficulties in launching the programme were compounded by the fact that, within AID, the interval between the decision to implement field programmes and their actual commencement was usually 3 years, and the Agency's procedures were geared to this pace. As time progressed, it became apparent that the single year allotted for preparation was unrealistic unless special measures were taken.

Fortunately, the recruitment of staff had been authorized and training could begin early in July 1966. Two basic categories of staff were recruited: medical officer–epidemiologists to provide overall assistance in programme development and execution, and non-medical personnel, termed "operations officers", who would deal with logistics—including the maintenance and repair of vehicles and jet injectors, the distribution of supplies and equipment and the handling of financial matters. Priority was given to persons in their twenties and thirties, who were considered to be more likely than older individuals to have the stamina and interest required for extended work in the field. This also reflected the view of African health officials, who argued that they had a very limited need for advisers, in the usual sense of the term, but required, instead, individuals who were willing to participate actively in field operations. One operations officer was recruited for each country and 1 for each of the 4 regions in Nigeria. One medical officer was recruited for each Nigerian region, 1 for each of the larger countries, and 1 for every 2 or 3 of the smaller countries—i.e., 1 for Dahomey and Togo, 1 for Cameroon and Gabon, 1 for Chad and the Central African Republic, and 1 for the Gambia, Mauritania and Senegal.

The medical officers were primarily epidemiologists who had worked in the USA with CDC or who had had international health experience. The operations officers included 4 with experience as United States Peace Corps volunteers, the rest having played an important role in CDC's domestic disease control programmes. The latter group, all of whom were university graduates, had received short-term training in epidemiology and disease control and had proved their merit in field control programmes. Their experience in programme management and field investigations was to prove invaluable. Although the operations officers were initially not well accepted by some senior government health staff because they lacked a medical degree, they rapidly earned respect and, in many areas, eventually served as senior advisers. So impressive was their performance that WHO increasingly recruited such persons for smallpox eradication and other programmes.

During the spring and summer of 1966, a manual for field operations was prepared from which the WHO *Handbook for Smallpox Eradication in Endemic Areas* (SE/67.5 Rev.1) was eventually adapted; other manuals dealing with the repair and maintenance of the jet injectors were prepared and tested in the field by Mr Morris; and orders were drawn up for the procurement of the necessary supplies and equipment.

Numerous problems were resolved during this period but a few of the more important and unexpected deserve mention. The licensing of smallpox vaccine for use in the jet injector caused one, wholly unexpected difficulty. CDC staff had assumed that the inoculation of vaccinia virus into the superficial layers of the skin by the jet injector's high-pressure spray achieved the same result as the administration of the vaccine by the scratch of a needle. However, in 1966, the agency in the USA responsible for biologicals—the Division of Biologics Standards asserted that the vaccine specially produced for the jet injector had to be treated as a new product and because it was intended for parenteral inoculation, it must be sterile. Vaccinia virus, however, was then being grown as it always had been on the flank of a calf, and when harvested it inevitably contained some bacteria. Subsequent steps in manufacture diminished the number of bacteria to very low levels, and tests were performed to ensure the absence of pathogenic species. It was impossible, however, to produce a vaccine which could be stated with certainty to be free of all bacteria unless it were grown in tissue culture. Vaccinia virus could be grown in tissue culture, but at that time no laboratory had succeeded in producing such a vaccine which met WHO's heat-stability requirements. The debate as to whether the vaccine for jet injection

had to be sterile spread from the USA to WHO, where those concerned with biological standards also proposed that vaccine intended for jet injection should be sterile. Although there was agreement that the issue was one of principle rather than perceived risk, those concerned with biological standards insisted that principle should take precedence over all other considerations. Faced with the prospect of having a thoroughly evaluated method for vaccination which was vital to the new programme, but no vaccine, CDC staff carried the debate to higher administrative levels within the United States Public Health Service and the World Health Organization and finally were able to gain agreement that, in this case, principle would not prevail. However, considerable time and effort were spent on resolving the problem—at the expense of other urgent activities.

The vehicles and their spare parts presented a second problem. CDC decided that standard model pick-up trucks rather than custom-designed vehicles were preferable and less costly, and that the refrigerators required for the transport of measles vaccine could simply be bolted to the bed of the truck. The most desirable were British or French vehicles, which were in common use throughout western and central Africa. Spare parts for such vehicles were already widely available and local mechanics were familiar with their necessary maintenance and repair. AID procurement policies, however, required the purchase of vehicles made in the USA, and efforts by CDC to obtain a waiver of this requirement were unsuccessful. To alleviate the problems of repair, arrangements were made with the manufacturer for all of the programme's professional staff to take intensive training in vehicle maintenance and repair. Spare parts had to be procured and specially stockpiled in all countries, but which spare parts and in what quantities was another question, since, curiously, neither the manufacturer nor the various agencies working in Africa, including WHO and UNICEF, had compiled a list of needed spare parts based on field experience. There was no option but to make a "best-guess" estimate of which spare parts to stock and, as might be expected, requirements only roughly approximated available stocks. Over time, and with special assistance from the manufacturers, the design of the vehicles was improved, special repair facilities were established and an effective transport system was ensured.

One of the most contentious problems related to the question of which of two measles vaccines should be procured—the Edmonston strain vaccine, which was produced by one manufacturer and which had been used since the 1961 campaign in Upper Volta, or a more recently licensed, more attenuated product, the Schwarz strain vaccine, produced by another manufacturer. The Schwarz strain vaccine resulted in less frequent and less marked febrile responses, but the initial antibody levels induced were lower (Krugman et al., 1965). The available evidence indicated that the two vaccines conferred comparable immunity but some investigators suggested that immunity following the use of the Schwarz vaccine might not be so long-lasting. Investigators in Senegal and Nigeria (Hendrickse et al., 1965) had evaluated the Schwarz strain vaccine and argued that it was the more desirable, given the fact that it would be administered to ill and malnourished children among whom the higher fevers caused by the Edmonston strain vaccine might be harmful. A number of African countries, however, encouraged by the manufacturer's travelling sales representative, requested the Edmonston strain vaccine. Even the *New England journal of medicine* (1965) entered the dispute, stating in an editorial, "... it may be wise, at least under circumstances such as exist in these countries [of western Africa], not to adopt other vaccines [other than the Edmonston strain vaccine] until the results of future studies become available". The manufacturer translated the editorial into French and circulated it widely in Africa, and eventually obtained support for the product from many United States legislators. One alternative for CDC was to permit each country to decide for itself which strain of vaccine would be used. However, CDC staff not only considered the Schwarz strain to be preferable, but for logistic reasons believed it important to employ only one type of vaccine. Eventually, the issue was decided by the United States Surgeon General, and ultimately all countries were persuaded to accept the use of this strain (which became routinely used). As with the standards for smallpox vaccine for use in the jet injector, the issue was satisfactorily resolved, but again at the expense of considerable time and energy.

The training programme began in July 1966. A month-long course in basic field epidemiology and biostatistics was followed by a month of specialized training which

covered subjects ranging from the history and socio-cultural characteristics of western and central Africa to the maintenance and repair of vehicles and jet injectors. To foster collaboration with WHO, the WHO advisers in Africa, Ladnyi and Dr Hans Mayer, were invited to participate during the first month of the course. When the course ended, however, the staff had to remain in Atlanta, housed in temporary and crowded quarters, because none of the national agreements had yet been signed.

Many discussions with governments about the programme had been conducted during the spring and summer of 1966 but, as has been noted earlier, formal agreements could not be signed at least until September. Nigeria was of the highest priority because of its size and because it was to serve as the site of the regional office. Nearly half the complement of technical staff were expected to live there. Nigeria, however, was then on the brink of civil war. A military *coup* in January 1966 had displaced the existing civilian authority, and 7 months later, a second *coup* coincided with an army mutiny in the north, during which thousands of Ibo tribesmen were killed. The Ibos, whose tribal home was eastern Nigeria, threatened to secede and to establish an independent nation. The signing of an agreement for a smallpox eradication measles control programme was not high on the list of the government's priorities. For many weeks, it appeared that the regional programme might well be doomed, as the United States Ambassador and the WHO Representative endeavoured, unsuccessfully, to obtain the agreement of the Nigerian government. Finally, Dr Lythcott flew to Nigeria to ascertain what might be done. The documents had been approved by the Minister of Health and awaited only the signature of the head of state.

Plate 17.4. CDC field staff received training in the maintenance and repair of vehicles in Atlanta before taking up assignments in western and central Africa. *Clockwise from lower left*: Margaret E. Grigsby, Ralph H. Henderson, Gordon E. Robbins, a vehicle maintenance instructor, Stanley O. Foster, Thomas Drake, E. Ademola Smith, William H. Foege, David Thompson, Donald Moore, Deane L. Hutchins, Hillard Davis, unidentified, Arlen Rosenbloom, Pascal Imperato, Bernard Lourie, Christopher D'Amanda.

During a 6-week period, Dr Lythcott, too, was unsuccessful in working through conventional channels but, at a social function, he was introduced to the President's fiancée. He explained the programme and the nature of his mission to her, and on the following day, the agreement was signed.

Nigeria's agreement, though it was crucial, was only one of 16 which were needed. In other countries, various problems delayed the signing of the programme agreements, and not until March 1967 was the last of these finalized. Agreement in principle to undertake a programme of smallpox eradication and measles control was more readily achieved than agreement on specific operational plans. CDC staff had envisaged a similar type of programme in all countries—in principle, an elaboration of the special mass vaccination campaign against measles. Mobile teams would use jet injectors in the administration of smallpox vaccination to everyone in the population, while measles vaccine would be given to children between 6 months and 4 years of age (Henderson, 1967). Expectations as to the extent of coverage to be achieved were modest—80% of the population in urban areas and perhaps 60% in peripheral areas. Important additional components, not then familiar to any of the countries, were the provision of independent assessment as a quality control measure to determine vaccine coverage and the success of vaccination, as well as a surveillance system utilizing detection sites such as hospitals and aid posts to measure progress in eliminating smallpox.

In countries in which mobile teams had previously been little used, or in which such teams had largely ceased to function, the plan was adopted with few changes. In most of the former French colonies, however, multipurpose mobile prevention units, often referred to as "prospection teams", were well established. As the teams moved from village to village on a planned itinerary they endeavoured to reach all parts of a country over a 2–3 year period, vaccinating the inhabitants against smallpox and sometimes tuberculosis and yellow fever and examining an average of 400–500 persons a day for leprosy, trypanosomiasis, yaws and (where the disease was present) onchocerciasis. The programmes, as well as many of the mobile units, were usually directed by French military medical officers. In these countries, separate programmes for smallpox and measles vaccination were seen

WHO / CHEVALIER

Plate 17.5. Jet injectors were used to administer smallpox vaccine in the left arm and measles vaccine in the right arm. Sometimes the injections were given simultaneously. Aluminium foil covers the vaccine vials to prevent the inactivation of virus by exposure to light.

to be wasteful of petrol and trained personnel. CDC staff, however, considered that the integration of the two programmes would present a problem because it would compromise the speed and efficiency of operations afforded by the jet injectors. In a population of 500, for example, fewer than 100 children would be of a suitable age to receive measles vaccine, a number barely sufficient to warrant the use of the injectors. A second problem was that the health officials in these countries saw no need to provide special teams to assess the results of the programme. Participation in the multi-purpose programmes was encouraged in most countries by giving individual certificates to persons examined and vaccinated by the teams, and by subsequently requiring these documents to be shown for administrative purposes. Because the prospection teams were well known to the people, and their activities were supported by local chiefs, health officials believed that no assessment was required other than to compare the numbers vaccinated by the teams with the estimated population in the area. A third problem was the reluctance of most authori-

ties to divert resources to improve reporting or to investigate cases of smallpox. This was considered to be wasteful because of the common view that the best that could be achieved was the control of smallpox as well as of measles; if a few cases of smallpox did occur they were thought of little consequence in the total context of health problems.

Compromises in the basic strategy were required. Support from the Secretaries-General of OCCGE and OCEAC—Médecin-Général Pierre Richet and Colonel René Labusquière, respectively—helped to resolve many problems. In the OCEAC countries, the smallpox eradication and measles control programmes were eventually fully integrated into the activities of the prospection teams (see box). In Upper Volta, the prospection teams continued to give smallpox vaccine but different mobile teams were created to give measles vaccine. In Côte d'Ivoire, separate measles vaccination teams and smallpox vaccination teams were formed (Table 17.3). In the other OCCGE countries, it was decided that special teams would conduct both smallpox and measles vaccination.

Few of the countries at first agreed to accept the provision of special teams to conduct independent assessments of smallpox vaccination coverage and takes. By the end of 1967, only 6 countries had created such teams—Dahomey, Ghana, Mali, Niger, Nigeria and Togo—although eventually 4 others did so—Chad, Gambia, Guinea and Sierra Leone. At the start, there was even less interest in smallpox surveillance, which fell by default to CDC advisers until late in 1968. Fortunately, assessment and surveillance were best accepted in the countries in which smallpox was the greatest problem.

When the first programme plan had been developed, in January 1966, it had been

Description of a Prospection Team in Action, Central African Republic

From a 1967 field report by Dr Ralph Henderson and Mr Neal Ewan:

"The team began its activities around 7.30 a.m. Zinga and an adjoining village were to be 'prospected' that morning. First, all the children between 6 months and 4 years of age were formed into a line and given measles vaccinations. They were tallied by age and sex as they received their shots. This procedure required about one-half hour, and took place with minimal difficulty.

"The team leader then requested the village to form into a line of males and a line of females. Each line then passed in front of a recorder, who tallied age and sex, and handed each person a metal tag from a box containing tags consecutively numbered from 1 to 1000. The line then moved through a small tent where a nurse performed a screening physical examination, particularly looking for trypanosomiasis, onchocerciasis, leprosy, and yaws. After passing through the tent, the line passed in front of the smallpox vaccination station, where everyone except infants under 3 months and pregnant women was vaccinated using the scratch technique. The line next moved to a table where each metal tag was collected, and yellow OCEAC cloth health certificates were given out, stamped with *rougeole* (measles) and/or *variole* (smallpox) and the date, and filled out with the person's name. People were then either dismissed or proceeded to one or more of three additional sites. Blood, sputum and stool specimens were obtained from suspects referred by the nurse performing screening physicals. The nurse concerned prepared slides to be read by one of two microscopists. Trypanosomiasis and onchocerciasis suspects were referred directly to the microscopists, who made their own slides from fluid and tissue obtained by placing a clean needle into suspected cysts or ganglions and wiggling it.

"The final member of the team dispensed drugs. Patients were either referred from the nurse doing screening physicals, or were passed along by the microscopists. Penicillin shots were given to yaws cases and their contacts. Chloroquine, aspirin and some antifungal skin ointments comprised the remainder of the basic pharmacy. Those with other diagnosed illness were referred to a local hospital or dispensary for treatment. By 11 a.m., about 250 people had been seen in this fashion, and the team packed up to move to the village where they would prospect on the following day."

Table 17.3. Western and central Africa: smallpox vaccination team operations in the attack phase (as at May 1969), by country[a]

Country	Special teams employed for:			Prospection teams	Number of teams	Average number of smallpox vaccinations per team-day[b]
	Measles vaccination	Smallpox vaccination	Measles and smallpox vaccination			
Cameroon				X	33	700
Central African Republic				X	7	..
Chad				X	13	1 000
Congo				X	8	..
Côte d'Ivoire	X	X			19	500
Dahomey			X		8	1 163
Gabon				X	9	250
Gambia			X		3	750
Ghana			X		10	3 000
Guinea			X		9	1 897
Liberia			X		6	377
Mali			X		13	1 000
Mauritania			X		6	..
Niger			X		14	1 500
Nigeria			X		72	3 000
Senegal			X		16	1 000
Sierra Leone			X		8	1 000
Togo			X		5	1 367
Upper Volta	X			X[c]	13	1 500

[a] Based on Millar & Foege (1969).
[b] .. = data not recorded.
[c] Smallpox vaccine only administered by prospection teams.

projected that "smallpox cases should cease by the end of the fourth year of the programme" i.e., by December 1970. In the autumn of 1966, projections were made as to the numbers of reported cases of smallpox which might be expected up to the end of the programme. This was done in the expectation that, with better recording, the reported incidence might actually rise during the first year of operations, thus generating concern on the part of the responsible administrators as to the effectiveness of the programme. Anticipating this problem, Henderson and his colleagues prepared a graph depicting the expected numbers of reported cases throughout the duration of the programme (Fig. 17.2). The graph is of interest, since the predicted incidence up to the end of 1968 was surprisingly close to what was actually found, but thereafter the results were substantially better than expected, one of the few occasions in which progress in the Intensified Smallpox Eradication Programme exceeded expectations.

One by one the programme agreements were signed, and personnel, supplies and equipment gradually began to arrive in western and central Africa. By March 1967, 16 months after the USA's decision to offer assistance, pilot projects had begun in 11 of the countries and a total of 2.5 million smallpox vaccinations had been recorded.

CHARACTERISTICS OF WESTERN AND CENTRAL AFRICA

The estimated 110 million population of the 19 countries included in the programme in 1967 inhabited a diverse ecological area ranging from humid tropical coastal areas with prolonged rainy seasons to rolling savanna and eventually to the vast, sparsely populated and arid Sahel, whose vegetation consisted of thorny scrub and stunted trees (Plate 17.6). Subsistence farmers formed the largest proportion of the population. Chris-

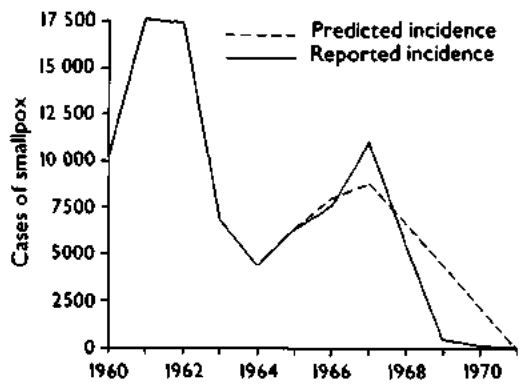
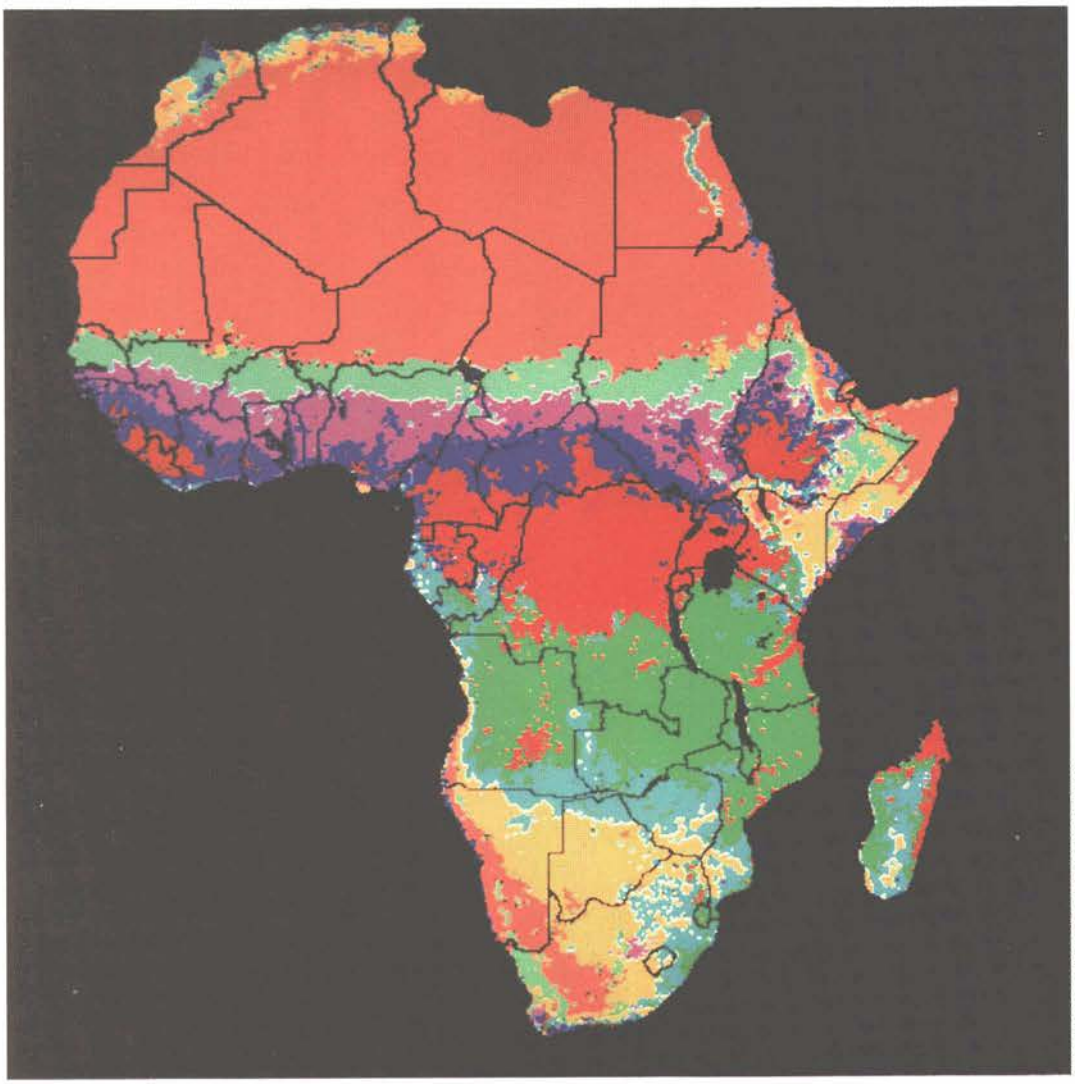


Fig. 17.2. Western and central Africa: number of reported cases of smallpox compared with the numbers predicted in September 1966.



NASA / GODDARD SPACE FLIGHT CENTER

Plate 17.6. Principal land cover components of Africa. The types of vegetation present in different parts of Africa were important in population distribution. Maps developed from satellite observations using very high-resolution radiometer sensors were prepared in 1982 (Tucker et al., 1985); the situation they show was probably not significantly different from that in 1967. The tan areas are desert and semi-desert, the light green are semi-arid wooded grassland, and the light blue are bushland and thicket; all these areas were sparsely populated. The purple areas are woodland and grassland, the dark green are woodland and the yellow are wooded grassland and thicket. The dark blue areas are interspersed tropical forest and grassland, and the red are tropical rain forest and mountain forest; the latter areas were more densely populated.

tians and animists lived primarily in the coastal areas; Muslim herders inhabited the Sahel. Tribes numbering from less than 100 000 persons to many millions, each with its own language, culture and customs, had traditional boundaries, often overlapping one or more national frontiers. In the process of evolving into nation-states, most countries experienced clashes between the new and the established and between religious, traditional, military and civilian leaders. Changes of government occurred frequently.

Paved roads provided limited links between coastal cities and some inland towns, but few connected the major capital cities. In the savanna, most unpaved roads were made of laterite, with a washboard surface that took a heavy toll of vehicles; in the coastal areas, there were clay roads, which were dusty during the dry season and a morass of mud during the rains. Railways were few and frequently out of order. Air transport connected many of the major cities and towns but schedules were followed erratically. Travel between one capital and another was sometimes more readily accomplished by flying by way of London or Paris. Similarly, telephone and telegraph links were generally few, and it was often easier to communicate with other countries through London or Paris.

The inhabitants of western and central Africa were inveterate traders and, despite poor roads, many travelled long distances to buy and sell cattle, textiles, salt, gold and other products. Local markets played an important role in commerce and as social centres. Some were held weekly, others at intervals of 4, 5 or 8 days. Herdsmen moved regularly across the Sahel seeking grazing areas and migrant labourers from the Sahel moved seasonally to coastal and savanna areas to harvest crops. Rapidly increasing urbanization characterized the entire area, the population of Abidjan (Côte d'Ivoire), for example, growing from 5000 in 1921 to 180 000 in 1966 and the population of Lagos (Nigeria) from 100 000 to 665 000 during the same period.

National administrative structures largely reflected the legacy of the previous British and French colonial administrations. In the former British colonies, the authority of the tribal chiefs had been supported and fostered within a decentralized civil structure; in the former French colonies, however, the power of the traditional chiefs was largely subordinated to that of the civil service and a strong centralized government. For the smallpox eradication–measles control programme, the support of the principal chiefs in the former British colonies was therefore as vital as that of the civil authorities; in the former French colonies, the civil service and village leaders provided the essential link with the people. The governmental structure was different in Guinea and Mali, where the authority of a national political party superseded that of traditional leaders. In both countries, the parties greatly facilitated contact with the villagers.

Approaches to the provision of health services also differed, depending on the colonial tradition. In the former British colonies, rural dispensaries operated by African personnel provided basic drugs and sometimes vaccine, but they were rather few and far between and their efforts were devoted primarily to curative medicine. The establishment of mission clinics and hospitals was encouraged, however, and in some areas these were quite numerous. In the former colonies of France, in contrast, health services were more widely available, through the use of mobile multi-purpose prospection teams. The system, conceived during the 1920s by Dr Eugène Jamot, had first been used to control trypanosomiasis in Ubangui-Shari (later the Central African Republic), but the teams' duties were gradually expanded to include the prevention and treatment of other diseases; in time, similar teams were organized throughout French West Africa and French Equatorial Africa (Richet, 1965; Cohen, 1971). The Service des Grandes Endémies, as the mobile service was called, provided basic health services in rural areas, supported by dispensaries, which served as treatment centres for patients referred by the mobile teams. The establishment of mission clinics and hospitals had not been encouraged and therefore not many existed. After the colonial period, health services continued to be supported in most countries by French bilateral assistance. Mobile teams were also used in some of the former British colonies for yaws control and occasionally for smallpox vaccination, but, except in Ghana (Waddy, 1956), they did not operate throughout the entire country.

Thus, in a number of the countries of western and central Africa, a structure and/or tradition existed for executing large-scale vaccination campaigns. Systems for the notification and investigation of cases, however, were poorly developed.

PLANS FOR THE PROGRAMME

With only 13 months allotted before the commencement of field operations, and with available personnel fully committed to working out the logistics, CDC staff had had no time to undertake feasibility studies, pilot projects or field reconnaissance to determine the extent of vaccinial immunity or to assess the epidemiology of smallpox or measles. A number of assumptions were made, some of which were later to prove erroneous. For example, it was assumed that vaccinial immunity was uniformly low throughout the region but, in fact, urban populations were later found to have been moderately well vaccinated, as were the inhabitants of large rural areas in some francophone countries. Especially low levels of vaccinial immunity were observed, however, throughout northern Nigeria, in many parts of Sierra Leone and in the more isolated rural villages in most countries. It was also believed that cases of smallpox would be found to be widely dispersed in all countries but, in fact, 10 out of the 21 countries in the region were found to be free of smallpox or nearly so by 1967. Where smallpox incidence was high, cases and outbreaks tended to be concentrated in specific geographical areas. It was also assumed that, as in Asia, the densely populated cities and market towns would constitute the major reservoir for the sustained transmission of disease, with spread occurring from these foci to rural areas (Henderson, 1967). It was discovered, however, that comparatively few cases occurred in urban areas but rural areas were found to be capable of sustaining transmission over surprisingly long periods.

CDC staff viewed the eradication of smallpox as a feasible objective given its epidemiological characteristics, but less was known about measles, since it was not routinely reported in most countries. However, control rather than eradication was foreseen because of the greater communicability of measles, especially in Africa (Morley, 1962; Senecal et al., 1962), the greater difficulty of clinical diagnosis and the fact that the disease had not been eliminated in any country, as of 1967, even in those with well-developed health services. Whether the objective of the programme should be defined in terms of the control of measles or its eradication had been debated at length. AID staff thought it preferable to establish eradication as an objective, believing that even if it was not achieved, more substantial progress would be made. CDC staff were concerned lest the enunciation of a goal which might prove to be unrealistic, as had been the case with malaria eradication (see Chapter 9), would only serve to erode further the credibility of public health professionals. Eventually, the CDC position prevailed and so the programme bore the somewhat clumsy title of "smallpox eradication–measles control" rather than the simpler "smallpox and measles eradication." As the programme was to demonstrate, effective measles control, let alone eradication, was a formidable task (United States National Communicable Disease Center, 1970; Foege & Eddins, 1973).

The planning process would unquestionably have benefited if more information had been available regarding the incidence of both smallpox and measles and the capacities of each of the national health services, but the seeking of such information would have caused a delay of perhaps 12–18 months. With many commitments already made, so long a delay was not acceptable. Moreover, because of possible changes of government staff and of priorities, there was no guarantee that a better-defined project would subsequently be approved for funding. Thus, with the resources at hand, there was a need to act. Consequently, the project began without preparatory studies, employing such information as was available; a great many assumptions were made in the hope that an able and energetic staff would solve problems as they arose.

It was recognized that the different characteristics of the administrative, health and social structures in each of the countries would dictate somewhat different types of programme. Therefore, instead of a highly prescriptive plan, four principles were formulated for the execution of the national programmes in the expectation that during the first year they would evolve by trial and error: (1) the programmes would be coordinated as a regional effort because of the ready movement of people across national borders; (2) freeze-dried vaccine would be administered by mobile teams employing jet injectors in order to economize on scarce resources; (3) independent assessment of the vaccination campaign would provide a quality control mechanism; (4) a workable surveillance programme would be developed on the basis of regular reporting from case-detection sites, because, as had been stated, "The goal of the

project is a specific one, the reduction of smallpox to the level of zero cases" (Henderson, 1967).

Surveillance, as a principle, was a characteristic which differentiated this from previous smallpox eradication programmes and eventually proved to be critical to its success. It was a concept that had been fostered by Dr A. D. Langmuir at CDC (see Chapter 9); since 1961, CDC's surveillance programme had been under Henderson's direction. With respect to smallpox, it was defined in the following terms (United States Communicable Disease Center, 1966):

(1) The routine, systematic collection of data, amplified appropriately by special field investigations and studies.

(2) The analysis and interpretation of reported data and studies on a concurrent basis.

(3) The initiation of appropriate definitive action, including field investigation, epidemic control, modification of operational campaign procedures, and recommendations regarding vaccination.

(4) Widespread dissemination of the compiled and interpreted data to principal reporting sources and to others concerned with disease control activities.

As has been noted earlier, the concept of surveillance was unfamiliar to health staff in western and central Africa and it was thought that not less than 2 years of sustained effort would be required to develop a surveillance system. The CDC *Manual of Operations* (United States Communicable Disease Center, 1966) pointed out the need to begin the development of a notification system from the inception of the programme but did not then envisage the obligation to investigate and contain all the outbreaks that were detected. As the manual stated:

"In countries with a high endemic occurrence of disease, field investigation activities may focus on comparatively few of the many outbreaks. As systematic vaccination programs progress, the importance of small outbreaks and individual cases becomes increasingly important. As the numbers of cases diminish, the field investigation and control procedures should be instigated for an increasing proportion and, ultimately, for all cases."

Three stages in the development of the surveillance programme were envisaged:

PHASE I Referring to endemic areas with a sustained or frequent high incidence of smallpox as indicated either by official reports or by educated estimates. This would include all countries with a rate of perhaps 1 or 2 cases or more per 100 000 population per year.

PHASE II—Referring to countries with a low continuing incidence of smallpox.

PHASE III—Referring to areas rendered non-endemic by systematic vaccination. No country or subdivision would be classified in Phase III until it had been covered by the attack phase of systematic mass vaccination.

Strategically, surveillance and containment activities in most countries were initially considered as subsidiary to mass vaccination, serving primarily to identify problems or weaknesses in the mass vaccination campaign. When the number of cases had been substantially reduced by the vaccination campaign, surveillance and containment would become essential to eliminate residual foci. The activities deemed appropriate for each phase of the programme are listed in Table 17.4. On the basis of the reported incidence in 1966, Phase I activities were called for in at least 6 of the countries—Dahomey, Mali, Niger, Nigeria, Sierra Leone and Togo.

EXECUTION OF THE PROGRAMME

The first year of the programme was to be devoted to formulating logistic plans, training national staff, and evaluating methodologies for adaptation by both national and CDC personnel. Although it was inevitable that the development of a programme of this magnitude would encounter substantial problems, their extent had not been anticipated. The solution of these problems by CDC ultimately became the responsibility of Dr Millar, who returned from study leave in the summer of 1966 and assumed direction of the programme on 1 November, when Henderson went to Geneva to head WHO's Intensified Smallpox Eradication Programme.

By September 1966, the recruitment and training of staff had been completed as scheduled, but little else was proceeding as planned. The procurement of supplies and equipment lagged far behind schedule and formal agreements with countries were slow to be concluded. Two countries refused to sign programme agreements until they had been formally assured that WHO would provide funds for fuel supplies and travel;

Table 17.4. Western and central Africa: surveillance activities at different phases of the programme[a]

	Phase I	Phase II	Phase III
Reporting	Emphasis on principal medical units to obtain regular reports. Progressive extension to include all medical and paramedical units.	Extension of surveillance network to ensure that detection sites exist in all parts of country and that reports are regularly submitted. Some telegraphic reporting of cases.	As in Phase II. All cases reported telegraphically.
Field investigation	Investigation of significant epidemics or epidemics in unusual areas as time permits.	All outbreaks promptly investigated by competent epidemiological authority. Cases promptly investigated by national or intermediate health jurisdictions. Case investigation forms submitted for every case.	Each case an "emergency". All cases promptly and routinely investigated by competent epidemiological authority.
Control procedures	Special units to undertake epidemic control as necessary.	Prompt control procedures for each case and outbreak by central or intermediate health authority.	Prompt control procedures with central authority participation. Identification, vaccination and, if necessary, isolation of contacts.
Laboratory study of cases	Only in special circumstances, usually for research purposes.	Specimens to be obtained from each isolated case and representative samples from outbreaks.	Every case to receive laboratory study.

[a] From United States Communicable Disease Center (1966).

several objected to the requirements for surveillance; another expressed concern about budgetary obligations; in Upper Volta, in which the measles control programme had first been successfully conducted, the director of the endemic diseases control service refused to endorse the programme on the grounds that smallpox eradication could not be achieved. Continuing discussions eventually led to the signing of 3 agreements in October, 4 in November and 3 in December. The last to be signed were those in the Gambia, Senegal and Upper Volta, in March 1967.

Each national programme experienced different types of problems and each had to be adapted to the health structure and social

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Plate 17.7. Health workers of Dahomey's endemic disease control service at a training course on the use of jet injectors, March 1967.

context of the country concerned. As programmes progressed, epidemiological observations and useful techniques for field operations were communicated from one to another through annual meetings of national directors and CDC advisers, through the travel of staff based in Lagos and Atlanta and through periodic surveillance reports which were sent to programme staff in all countries. To attempt to present events throughout the region in chronological order is difficult and confusing, given the number of different national programmes. Accordingly, we shall first describe progress in the programme as a whole before commenting on the salient features of individual national programmes.

In most of the countries, field operations commenced between January and June 1967; in the others, for which assistance had been postponed for a year—Guinea, Liberia and Sierra Leone—these operations had all begun by January 1968.

The proposed method of operation in each of the vaccination campaigns drew extensively on the experience of Dr Harald Frederiksen, a United States adviser to an earlier successful smallpox vaccination campaign in Bolivia (Frederiksen, 1962). It called for vaccination of the population at assembly points. This was achieved through preparatory meetings with local chiefs and civil authorities to explain the programme and to solicit their help. Such meetings took place 1 to 7 days before the vaccination team arrived. The assembly points were usually selected so that no one would have to walk more than 8 kilometres, although, in some areas, even this distance was found to be too great and it was decreased to 3 kilometres. The teams usually consisted of 5 or 6 persons—as many as could conveniently ride in one vehicle. They vaccinated all persons against smallpox and children between 6 months and 4 years old against measles. Although on some days as many as 10 000–14 000 persons could be vaccinated, on average the teams administered between 750 and 3000 smallpox vaccination daily (Millar & Foege, 1969) and about one-fifth of this number of measles vaccinations. The teams usually worked for a consecutive 3-week period, camping out or staying in the villages. As experience demonstrated, living among the local population fostered cooperation and improved vaccination coverage. At the end of the 3 weeks, 7–10 days were set aside for rest and recuperation.

Jet injectors were used for most vaccinations, but in small villages and among special groups, smallpox vaccine was administered by bifurcated needle. Most people readily accepted vaccination, although resistance was encountered in Dahomey, Togo and south-western Nigeria, where an animist cult was active among some small groups, and in scattered, remote areas. In each instance, special efforts were made to persuade village and religious leaders of the benefits of vaccination—usually, but not always, with success.

In urban settings, the vaccination campaign required special planning and the provision of many more vaccination assembly points. In Nigerian towns, it was calculated that one assembly point would be required for every 8000 persons and that arrangements would have to be made for vaccination in the early morning and late afternoon (Smith et al., 1970). The most intensive urban campaign was that conducted in Ibadan (Nigeria), in which, over a 10-day period, 12 teams administered 757 308 smallpox vaccinations and 69 069 measles vaccinations. People connected with the university, local churches and private voluntary organizations, as well as members of the police force, assisted in the effort.

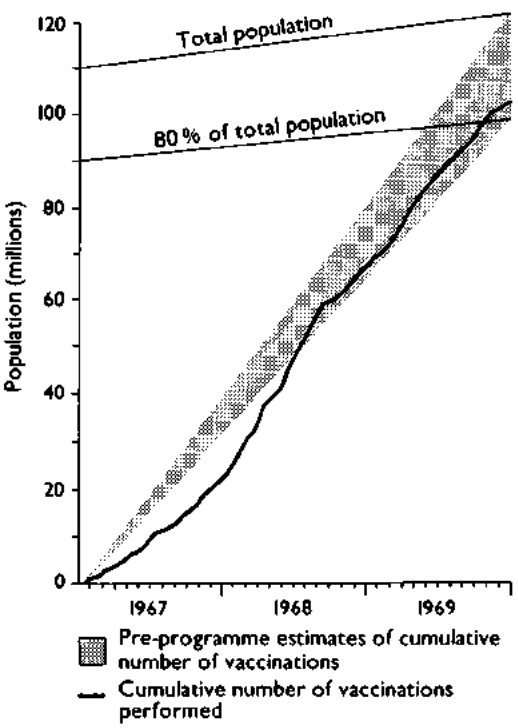


Fig. 17.3. Western and central Africa: cumulative number of vaccinations performed compared with pre-programme estimates. (From Foege et al., 1975.)

Plate 17.8. William Stewart, Surgeon General of the United States Public Health Service, attended a special ceremony in Ghana, in January 1968, to celebrate the 25 millionth vaccination given. George Lythcott (b. 1918), with sunglasses, was Director of the CDC regional office in Lagos from 1967 to 1972. An able and diplomatic administrator, Lythcott played an important role in sustaining the momentum of the programme through many political and logistic crises.

The pace of the vaccination campaign gradually accelerated. By January 1968, a special ceremony in Ghana marked the 25 millionth vaccination and by the summer of 1968 (Fig. 17.3), the numbers vaccinated had reached the optimistic estimates of January 1965.

The concurrent assessment of coverage, although deemed essential, was conducted in only 9 of the countries. The principal objection to assessment was that it wasted resources. Where it was performed, teams of 2 or 3 persons visited a random sample of 5–10% of the villages whose inhabitants had been vaccinated 4 10 days previously to ensure that the proportion of successful vaccinations was satisfactory and that coverage was adequate. Where coverage was found to be low, a repeat vaccination campaign was organized. Assessment data showed that good coverage was achieved in most countries (Table 17.5).

To ascertain the overall efficacy of the vaccination campaign, special surveys were conducted in 1968 in 5 areas—Dahomey, Niger, northern Nigeria, western Nigeria, and Togo under the direction of Dr Ralph Henderson, then deputy director of the Lagos regional office (Henderson et al., 1973). With Mr Donald Eddins and Dr William Foege, he devised for the purpose of this survey a practical method of cluster sampling based on principles elaborated by CDC statisticians for immunization surveys in the USA (Serfling & Sherman, 1965). (The method was later adapted for use in WHO's Expanded Programme on Immunization, in nutrition surveys and in other health status assessments.) The survey revealed a generally satisfactory performance in most programmes. Nearly 80% of the people questioned reported having been vaccinated with jet injectors (Table 17.6). The low rates among those under 1 year of age

Table 17.5. Western and central Africa: selected coverage figures for countries carrying out systematic assessment, 1969, by age[a,b,c]

Country	Percentage vaccinated in age group (year):					Take rates in age group 0–4 years
	0–4	5–14	15–44	⩾45	All ages	
Chad	63	74	83	88	78	100
Ghana	94	96	93	80	93	93
Guinea	91	94	88	85	90	99
Liberia	84	92	88	82	83	100
Mali	100	93	94	96	95	..
Niger	82	90	67	26	74	100
Nigeria[d]	91	86	68	..	77	..
Sierra Leone	90	89	80	74	84	100

[a] Based on Millar & Foege (1969).
[b] .. = data not recorded.
[c] Assessment was also carried out in Togo, but no data are available.
[d] Data for Gombe town, North-eastern State, in age groups 0–3, 4–14, and ⩾15 years.

Table 17.6. Western and central Africa: results of cluster sample surveys in five areas, 1968–1969: (A) by age; (B) by country or area

A. By age

Age group (years)	Percentage of population:		
	With history of vaccination by jet injector	With vaccination scar	With pockmarks
<1	33	30	1.7
1–4	82	79	1.3
5–14	88	90	4.7
15–44	78	87	19.6
⩾45	67	75	21.9
All ages	77	82	12.8

B. By country or area

Country or area	Percentage of population:		
	With history of vaccination by jet injector	With vaccination scar	With pockmarks
Dahomey	71	80	8.3
Niger	79	79	5.5
Nigeria, northern	88	84	25.6
Nigeria, western	60	76	9.3
Togo	80	88	3.1

could largely be accounted for by children born after the mass campaign; lower rates among those over 45 years were attributable to the fact that a number of older people had declined to be vaccinated, believing (correctly, in most instances) that they were already immune owing to previous disease or repeated vaccinations. The best results were obtained in northern Nigeria, in which cooperative, authoritarian emirs and district chiefs directed their subjects to accept vaccination; the lowest rates were found in western Nigeria, which lacked the tradition of authoritarian leadership and in which no concurrent assessment had been conducted.

Special comment is called for regarding the results obtained among children aged 0–4 years in Niger and northern Nigeria. In these areas, the proportion with a vaccination scar acquired at any time was lower than the proportion reported to have been vaccinated with the jet injector. This paradox can be partly explained by the possibility that some of the vaccinations by jet injector might have been unsuccessful or that parents might have reported that vaccinations had been performed when they had not. Because the surveys were conducted many months after the campaign, it proved impossible to determine the cause or to remedy the situation.

Of particular interest was the much higher proportion of persons in northern Nigeria with facial pockmarks, confirming a growing suspicion that this was the principal endemic focus of smallpox in western and central Africa.

Coordination With International Organizations

Throughout the course of the programme, beginning with the initial planning visits, efforts were made by CDC staff to develop a collaborative working relationship with WHO through its Regional Office for Africa, the WHO representatives in the respective countries and two WHO smallpox advisers based in western Africa—one in Mali and the other in Liberia. These attempts were less successful than had been hoped, partly because the WHO regional adviser in Brazzaville who had been assigned responsibility for smallpox eradication had many other duties and could devote little time to the programme. Dr Mayer, the WHO adviser in

Measles Control

Many valuable observations were made during the course of the programme with respect to the epidemiology and control of measles (Foster & Pifer, 1971), a disease which presented quite different problems from those of smallpox. Case-fatality rates associated with measles were customarily 4–5%, sufficient to identify it as second only to malaria as a cause of death among children. In contrast to smallpox, measles spread rapidly and widely. Studies in urban and in the more populous rural areas revealed that 50% of cases occurred in children less than 15 months of age (Smith & Foster, 1970a). Only in remote villages, where visitors were infrequent, did substantially higher proportions of cases occur among older children (Millar, 1970). In densely populated urban areas, morbidity decreased by about half for only 1 year following a mass vaccination campaign; in more sparsely populated areas, this decrease persisted for 2 years but the incidence then returned to pre-vaccination campaign levels (Smith & Foster, 1970b). In the hot and humid densely populated coastal areas, there was no apparent seasonal change in the frequency of transmission.

The prevention of measles infection was, and continues to be, a difficult problem. Essentially all children are born with circulating maternal antibody, which prevents infection. In some the protection is lost within 5 months, but in others it persists for up to 12 months of age. However, immunization is successful only after maternal antibody is lost, this antibody serving to protect against the attenuated infection induced by the measles virus vaccine. To prevent infection, therefore, it is necessary to administer the vaccine during the brief period between the time the child has lost the protection conferred by maternal antibody and his exposure to infection—in Africa, usually between 6 and 18 months. In a mass campaign in which vaccinations are given, for example, every 2–3 years to preschool children, much of the vaccine has no effect, these children being protected by maternal antibody or having already had the disease. Thus, the effect of a mass campaign on measles incidence is a transitory one. Efforts were made to vaccinate at more frequent intervals in urban areas of western Africa, but usually this had little effect unless the campaigns were conducted every 6 months, a prohibitively expensive strategy. Vaccination at conveniently located health centres was an alternative but in most areas there were few of these and most were not equipped with refrigerators. Thus, although the number of measles cases and deaths could be reduced, sometimes substantially for short periods of time, long-term control was not achieved.

Liberia, was WHO's intercountry adviser for all smallpox programmes in western and central Africa, but he could rarely travel. In 1968, he was transferred to Mauritania, where he served as the smallpox eradication programme adviser, the CDC adviser having had to leave Mauritania when diplomatic relations between that country and the USA were severed. The WHO adviser assigned to Mali rarely left the capital and in 1968 his post was discontinued. In response to requests from Member governments, the WHO Regional Office for Africa provided funds to cover local costs, 13 countries receiving in all a total of US$1 110 675 over the period 1967–1972. However, apart from processing these requests, the regional office and the WHO country representatives had little contact with the CDC programme.

From Geneva, Henderson maintained close contact with the CDC staff in Atlanta. They and selected national counterparts contributed to WHO interregional and intercountry smallpox seminars in Africa, South America and Asia; some WHO staff from the regions participated in the CDC smallpox eradication training programme in Atlanta in 1967 and 1968; and accounts of the progress made in western and central Africa were regularly published in the WHO *Weekly epidemiological record* and in special reports of the smallpox eradication programme. From 1968, supplies of bifurcated needles began to be shipped from Geneva, and in 1969 a jointly sponsored

WHO/AID/CDC conference on smallpox eradication was organized in Lagos. The extensive proceedings, which documented many important observations on smallpox eradication (United States National Communicable Disease Center, 1970), were distributed to WHO and national staff throughout the world.

Collaboration with OCCGE and OCEAC was effective and useful. These organizations, both supported by France, kept abreast of events through written reports and discussions at their semi-annual meetings, which dealt with the progress and policies of this and other regional programmes. The directors of these organizations also participated actively in solving problems of implementation and communication arising in programmes conducted by their member governments. In addition, OCEAC served as an intermediary for the transmittal of national reports and the receipt of supplies and equipment for the Congo, with which the USA did not then have formal diplomatic relations; beginning in 1968, OCCGE performed a similar function with respect to Mauritania.

Changing Roles of the CDC Atlanta Office and the Lagos Regional Office

Flexibility in the management structure was no less important than in field operations. The Lagos regional office had been expected to serve as the principal point of contact for operations and as the conduit for reports and requests from all the national programmes; the CDC Atlanta office was expected to bear primary responsibility for recruitment, training, procurement of supplies and equipment and liaison with AID. This management relationship had originally appeared to be the most logical because of the geographical proximity of the Lagos office staff to field operations and of the less elaborate procedures that would be needed to obtain United States government approval for travel by persons stationed abroad. What had seemed logical during the planning stage, however, proved less functional in practice. It soon became apparent that communication between the individual countries and Atlanta was usually easier than between them and Lagos. When a protracted civil war broke out in Nigeria in 1967, the difficulties became greater as cable traffic increased. Because messages concerned with the smallpox eradication–measles control programme were given low priority, a cable from a national capital sent through Lagos took as long as 1–2 weeks to reach Atlanta. Shipments of supplies by air freight or diplomatic pouch were also delivered more promptly when dispatched from Atlanta than from Lagos. Although it was a major transport centre, Lagos had few direct flights to many of the African capitals, especially those of the francophone countries. In consequence, field staff and personnel in Atlanta, faced with an increasing array of problems, found it necessary to communicate direct with each other.

Towards the end of the first year, responsibilities and relationships were redefined to centralize direction in Atlanta, the Lagos office assuming a support role in contacts with national authorities and undertaking special investigations and assessments. In practice, the revised system worked well: new approaches were identified as experience accrued, and alternative methods and systems found useful in one country were applied with little delay throughout the region.

Surveillance and Containment Activities

It had been thought at first that surveillance and containment activities would be most crucial to interrupting transmission during the concluding phases of each of the national mass campaigns, but experience quickly showed that they could play a vital role from the beginning of a programme, irrespective of smallpox incidence. This was first shown in eastern Nigeria, just as the regional programme began.

The Nigerian programme agreement was signed on 6 October 1966 and field staff soon began to arrive. Operations were, however, initially confined to 2 of Nigeria's 4 regions because special agreements had to be finalized with each of the semi-autonomous regions before work could begin. The Eastern Region was the first to commence operations. In November 1966, Dr Foege with Dr David Thompson and Mr Paul Litchfield, began a programme of staff training while awaiting delivery of vehicles and other commodities. Early in December, they were informed by a missionary of smallpox cases in a small village and decided to use this opportunity to train vaccination teams in containment activities. Using borrowed transport, they vaccinated people in the

village and along nearby roads; an outbreak of 19 cases was stopped in 4 weeks (Foege et al., 1975). Missionaries in the southern part of the Eastern Region, who had their own radio network, were approached for help in notifying other outbreaks. Two further outbreaks were soon identified, one of 14 cases and one of 5 cases. Both were contained within 3 weeks, again simply by vaccinating household and village contacts. With the limited resources available, the programme staff had expected to do little more than control a few of an anticipated large number of outbreaks, but surprisingly no further outbreaks were reported in this area. On investigation, the staff discovered that the last epidemic to be recorded in the area had occurred in 1950, despite the fact that comparatively few persons, except those living near roads, had been vaccinated since then. The first case in the 1966 outbreaks had come from the Northern Region of Nigeria fully 5 months before; subsequently, smallpox had spread slowly southwards with as many as 4 generations of cases occurring in a single compound. The finding of so few outbreaks, all in nearby villages, along with the discovery that they could be rapidly contained even where vaccinial immunity was low, was impressive. A review of data from earlier years suggested that outbreaks normally began along the northern borders of the region and spread progressively towards the south, an observation which suggested that persistent endemic transmission did not occur in most of the Eastern Region.

The programme staff decided to concentrate their resources in areas in which smallpox was known to be present. Accordingly, a new reporting system was devised. In each of the 3 provinces of the Eastern Region, a reporting officer was designated to obtain weekly reports from all government and missionary health establishments and transmit them by radio directly to Enugu, the regional capital. The data quickly revealed that most of the known cases were occurring along the northern boundaries, and a pilot vaccination campaign was therefore begun in the northern urban area of Abakiliki (WHO/SE/68.3, Thompson & Foege). Within a week, 46 500 people were vaccinated and gradually the campaign moved to adjacent areas in the savanna. Numerous unreported cases of smallpox were discovered and, by May 1967, 754 cases with 180 deaths had been documented.

Meanwhile, political turmoil steadily increased throughout the Eastern Region and on 30 May the predominantly Ibo tribal population seceded from Nigeria, proclaiming the independent Republic of Biafra. It became increasingly difficult to continue with the programme; travel was restricted to those with special passes, and petrol became scarce. Nevertheless, during June 1967, a mass vaccination campaign was conducted in and around Enugu — the only remaining endemic focus. By the end of the month, transmission appeared to have ended, after only 6 months of activity, during which only 750 000 of the 12 million inhabitants had been vaccinated (Foege et al., 1971). Programme operations in eastern Nigeria were interrupted almost immediately thereafter but the idea had been planted that it might be desirable to give precedence to the discovery and containment of outbreaks over the execution of the mass vaccination campaign.

By June 1968, vaccination teams were active in 19 countries; some 40 million persons had been vaccinated—about 35% of the estimated population. In each programme, priority was given to vaccination campaigns in the areas reporting the most cases of smallpox, although this strategy was not pursued with the same vigour as in eastern Nigeria. Less than half the countries had independent assessment teams but in most of them documentary or other evidence indicated that the vaccination coverage was high. The impact of the vaccination campaign was already apparent, only 2312 cases being reported by the end of May compared with 4071 during the same period of the preceding year. Although reporting systems were still inadequate, many cases which would not otherwise have been reported were being detected by vaccination teams, and some during outbreak investigations, where these were being undertaken.

In June 1968, Dr Foege, who had joined CDC's Atlanta staff, proposed to participants at the annual CDC Regional Programme Conference a change in strategy to hasten eradication — namely, to give priority to the detection and containment of outbreaks (Foege et al., 1971). Originally, there had been doubt that simple containment measures could be effective because of the common belief that smallpox was comparatively easily and rapidly transmitted through the population (Felsenfeld, 1966; Top, 1968), especially where vaccinial immunity was low. The

experience in eastern Nigeria and a study in Dahomey in 1967 (Henderson & Yekpe, 1969) contradicted this. Moreover, epidemiological studies of smallpox in East and West Pakistan in 1966–1967 (Thomas et al., 1971a,b, 1972; Mack et al., 1972a,b) also showed that smallpox spread slowly, that outbreaks tended to be clustered in an area rather than widely dispersed and that at the low point of seasonal incidence very few villages were infected. These observations were also confirmed in India in a study conducted in a district classified as heavily infected but in which it was found that at no time were more than 1% of all its villages infected with smallpox (India National Institute of Communicable Diseases, 1968).

Dr Foege reasoned, as had the investigators in Pakistan, that intensive efforts to detect and contain outbreaks, if begun at the low point of seasonal incidence (September–October), should readily contain the few outbreaks then present. This would serve to avert major epidemics later in the year, when smallpox spread more rapidly. He proposed that each of 8 countries which then had endemic smallpox should undertake an intensive and continuing programme of surveillance and containment. The programme was given the name E^2, for "eradication–escalation" (Foege et al., 1971). The strategy was formally adopted in July 1968 by all countries except Nigeria, which decided that because of a widening civil war, it would give priority to completion of its mass vaccination campaign. However, in areas of Nigeria in which mass vaccination had been conducted, specially assigned short-term CDC epidemiologists would undertake outbreak investigation and containment.

For the detection of cases, the usual reporting mechanism was augmented by the cooperative efforts of other special health service programmes (e.g., leprosy and malaria control), government personnel, village leaders and non-governmental bodies such as missions. Outbreaks were investigated and vaccination was performed in a "geographically or socially contiguous area around each patient", as determined by epidemiological investigation. The area was not defined more explicitly, as was later done in Asia, nor was an attempt made to enumerate contacts and village populations to ensure that all had been vaccinated.

The increase in surveillance activity led to the discovery of many additional cases, with the result that the number of reported cases rose from 197 in August to 289 in September; from then on, it fell steadily (Table 17.7).

By January 1969, endemic smallpox remained only in Dahomey, Nigeria, Sierra Leone and Togo. The last cases in Sierra Leone and Togo were detected in May of that year, and the last case in Dahomey was found in September; thereafter no further cases were notified for 6 months (Table 17.8). In March 1970, however, a persistent endemic focus was discovered in northern Nigeria, but 2 months later the last known case in Nigeria, the last in western and central Africa, was detected, only 9 months after "eradication–escalation" had begun.

The vaccination campaign continued throughout the "eradication–escalation" operation, 33 million persons being vaccinated during 1969 and 22 million in 1970 (Table 17.9). Contrary to expectations, the pace of the vaccination campaign did not diminish during this period; indeed, more vaccinations

Table 17.7. Western and central Africa: number of cases of smallpox reported and detected in 9 countries,[a] 1968[b]

Period	Total	Number of reported cases	Number of additional cases discovered	Percentage detected through active surveillance
January–June	4 060	3 865	195	5
July–September	828	612	216	26
October	265	88	177	67
November	215	69	146	68
December	140	60	80	57

NOTE: These data, taken from field records, differ somewhat from the figures given in official reports, from which for example Table 17.1 was compiled.

[a] Cameroon, Dahomey, Guinea, Mali, Niger, Nigeria, Sierra Leone, Togo and Upper Volta.

[b] Based on Foege et al. (1971).

Table 17.8. Western and Central Africa: number of reported cases of smallpox by country[a] and by month, 1969–1970

Country	1969[b]												1970[b]					
	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	March	April	May	June
Cameroon	1[c]	2[c]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dahomey	3	0	0	0	0	0	31	12	12	0	0	0	0	0	0	0	0	0
Guinea	16[d]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mali	0	1[c]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Niger	2[c]	5[c]	14[c]	1[c]	0	6[c]	0	0	0	0	0	0	0	0	0	0	0	0
Nigeria	78	58	15	9	13	16	5	0	0	(2)	(3)	(4)	(1)	(27)	(28)	(7)	(3)	0
Sierra Leone	23	30	3	14	10[e]	0	0	0	0	0	0	0	0	0	0	0	0	0
Togo	13	6	3	51	10	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	136	102	35	75	33	22	36	12	12	2	3	4	1	27	28	7	3	0

[a] No other countries in western and central Africa reported cases after 1968.
[b] Figures in parentheses denote cases recorded by date of onset rather than by date of notification; these cases were discovered on 21 March and during succeeding weeks.
[c] Reported to be importations from the Northern Region of Nigeria.
[d] Cases reported in January 1969; the onset of the last case was in December 1968.
[e] Cases reported in May 1969; the onset of the last case was in April 1969.

were given each week, on average, than before the special programme began. By the end of 1970, the number of vaccinations performed in 12 of the countries was equivalent to, or greater than, the estimated population.

During 1971–1972, the programme was modified in order to give priority to the vaccination of those who had been missed during the initial mass campaign and of those born after it. By the end of 1972, 153 484 000 smallpox vaccinations and 28 163 000 measles vaccinations had been performed. The cost of smallpox eradication in the region was estimated to be US$0.138 per head of population (Foege et al., 1975).

In 1972, as the 5-year programme drew to a close, CDC staff proposed to AID that other types of vaccine and support for other preventive measures should be provided in order to strengthen the health services in the countries of western and central Africa. Although the proposal was endorsed by all the ambassadors of the USA in the region, as well as the respective health ministers, the programme was terminated at the end of 1972. CDC sought to sustain surveillance and a maintenance vaccination programme by assigning epidemiologists to OCCGE and OCEAC, but because of the large number of countries and the lack of supplies and equipment to replenish the programmes, vaccinial immunity steadily declined thereafter as did the quality of surveillance. By 1976, when precertification activities had to be undertaken, special programmes had to be initiated in all the countries of the region to document what had been accomplished and to verify, through pockmark surveys, that no further cases had occurred.

NATIONAL PROGRAMMES

Each of the national programmes had different characteristics and encountered different types of problems, some of which are summarized and discussed below. For ease of presentation, the countries are dealt with in 7 groups (shown in Fig. 17.1): (1) Nigeria—the most populous country, which, between 1967 and 1970, reported 6854 (40%) of the region's 17 106 cases; (2) Dahomey and Togo—2 small adjacent coastal countries, in which smallpox incidence was high, and in which there was resistance to vaccination because of fetish practices; (3) Mali, Niger and Upper Volta—3 inland Sahelian countries, in which

Guinea-Bissau

Throughout the duration of the AID-supported smallpox eradication programme in western and central Africa, the status of smallpox in Guinea-Bissau was uncertain and caused concern. Until 1974, when Guinea-Bissau became independent, the Portuguese colonial administration reported regularly that no smallpox cases had occurred. However, there was widespread civil war, with rebel forces reputed to be in control of two-thirds of the country. The adjacent country of Senegal remained smallpox-free and posed no threat, but extensive epidemics occurred in many parts of Guinea, in which the bases of the rebel forces were located. Officially, nothing could be done to support activities in Guinea-Bissau but, as was the case in the Sudan, which also experienced protracted civil war (see Chapter 18), leaders of the rebel forces evinced concern about smallpox. They sent health workers for training in Guinea, which provided vaccine and bifurcated needles. Health staff in the rebel-held areas also reported periodically on smallpox. So far as could be ascertained at the time, and later during certification surveys, no cases of smallpox occurred in Guinea-Bissau during this period.

there were many nomads and frequent transhumance; (4) Guinea and Sierra Leone—2 highly endemic countries, in which programmes were launched nearly a year later than in the other groups but which succeeded in interrupting transmission within 18 months; (5) Côte d'Ivoire, Ghana and Liberia—3 adjoining countries on the southern coast of western Africa, which experienced few cases of smallpox after 1966; (6) the Gambia, Mauritania and Senegal—all of which were free of smallpox when the programme began, and remained so; and (7) the OCEAC countries—only 2 of which (Cameroon and Chad) detected cases of smallpox after 1966, mostly imported from Nigeria. Guinea-Bissau's status is summarized in the accompanying box; activities in Equatorial Guinea, which remained free of smallpox and in which no special programme was conducted, are not further described.

CENTRE CULTUREL AMERICAIN, COTONOU

Plate 17.9. A vaccination team at work in Dahomey in 1967.

Nigeria

Nigeria (population in 1967, 51.9 million) was the crucial country for the smallpox eradication programme, being centrally located and heavily endemic (Fig. 17.4) and having a population totalling nearly half that of the entire region. The largest number of CDC technical staff were therefore assigned to Nigeria and the CDC regional programme office was located there.

When the programme began, Nigeria was a federal republic consisting of 4 regions and the federal district of Lagos. Because responsibility for health matters was delegated to the

Table 17.9. Western and central Africa: number of reported smallpox vaccinations (thousands), by country, 1967–1972[a]

Country	Population in 1967[b] (thousands)	Year[c]						Cumulative total of vaccinations Jan. 1967–Dec. 1972
		1967[d]	1968[d]	1969	1970	1971	1972	
Cameroon	6 371	1 611	1 996	1 693	**1 443**	3 250	2 215	12 208
Central African Republic	1 785	381	405	477	508	**558**	427	2 756
Chad	3 458	1 386	1 345	**1 322**	1 182	977	666	6 878
Congo	1 125	162	581	312	**617**	288	73	2 033
Côte d'Ivoire	4 903	1 580	1 756	**1 582**	548	619	67	6 152
Dahomey	2 546	702	990	**934**	849	448	184	4 107
Equatorial Guinea	278	..	..	82	**238**	15	6	341
Gabon	923	225	146	175	201	105	**138**	990
Gambia	438	231	147	40	**40**	20	3[d]	481
Ghana	8 107	1 342	1 988	2 094	1 909	**1 052**	481[d]	8 866
Guinea	3 699	1 068	2 063	**1 434**	1 453	1 200	1 100[d]	8 318
Liberia	1 258	44	231	398	191	120[e]	268[e]	1 252
Mali	5 330	1 043	1 472	1 193	516	56	111	4 391
Mauritania	1 158	..	0	426	202	193	297	1 118
Niger	3 895	1 610	1 166	936	**1 297**	850	776	6 635
Nigeria	51 929	9 560	23 494	16 155	**8 702**	5 362	5 454	68 727
Senegal	3 675	383	1 468	762	330	507	124	3 574
Sierra Leone	2 720	0	965	1 154	258	93[e]	100[e]	2 570
Togo	1 774	605	608	**922**	467	507	166	3 275
Upper Volta	4 815	2 040	2 208	**1 338**	1 026	1 568	632	8 812
Total	110 187	23 973	43 029	33 429	21 977	17 788	13 288	153 484

[a] Based on Foege et al. (1975).
[b] Population data from United Nations (1985).
[c] Figures in bold type indicate the year in which the total number of vaccinations performed after 1966 equalled or exceeded the estimated population.
[d] .. = data not recorded.
[e] Incomplete and/or provisional data.

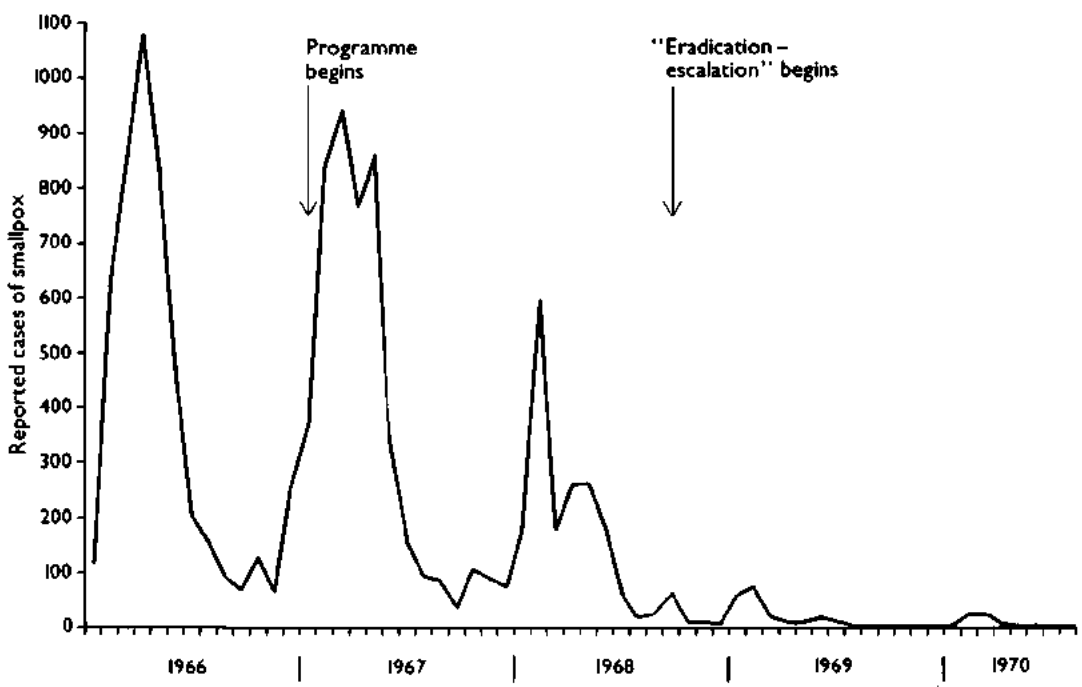


Fig. 17.4. Nigeria: number of reported cases of smallpox, by 4-week period, 1966–1970.

regions, programme policies and plans had to be worked out and agreed on not only at the federal level but with each regional authority as well. Each region, in turn, dealt with traditional tribal authorities, which, in the Northern Region, had substantial powers. The National Council on Health had decided in 1962 that the eradication of smallpox should be an objective of national policy (Foster & Smith, 1970) and plans for such a programme were developed by the Principal Medical Officer of the Ministry of Health of Nigeria, Dr G. A. Ademola. Implementation of the programme, however, had to be delayed until 1967, when resources were made available by AID. Meanwhile, thermolabile lanolinated vaccine, produced in a government laboratory in Lagos, was provided for use in health centres, but because it was rarely kept under refrigeration, many of the vaccinations were unsuccessful. Mobile field teams, which periodically undertook mass vaccination campaigns, undoubtedly improved vaccinial immunity in the Eastern, Western and Mid-Western Regions. However, nowhere was the level of immunity high, and in the Northern Region, vaccination coverage was especially poor.

Pockmark surveys conducted after the AID-supported programme began revealed that smallpox had been widely prevalent throughout Nigeria during the early 1960s, an estimated 100 000 or more cases having occurred annually. Survey data, as well as morbidity data compiled in 1967 (Fig. 17.5), showed the Northern Region to be the most heavily afflicted. In this region, which consisted mainly of savanna and arid scrub, the highest incidence occurred in the dry season, from January to May; in coastal areas, seasonal changes were less marked. The case-fatality rate was probably about 10%, although the only available data pertain to persons admitted to hospital—usually those who were the sickest and among whom deaths would have been more frequent (Table 17.10).

Early in 1967, Nigeria was on the brink of civil war. As major tribal groups vied for power, a military government displaced civilian rule, and an army mutiny occurred in the north, accompanied by extensive riots. The Eastern Region of the country threatened to secede. Despite these serious problems, the government supported the smallpox eradication programme. Pilot activities, each with its own programme unit, began in Lagos and in the Eastern and Western Regions during the spring of 1967 and in the Northern and Mid-Western Regions during the summer. Because of the widespread prevalence of smallpox and concern as to the continuing stability of the country, Dr Ademola and Dr Stanley Foster, the CDC senior adviser, decided to devote all available resources to the mass vaccination campaign, giving first priority to the areas with the highest incidence in each region.

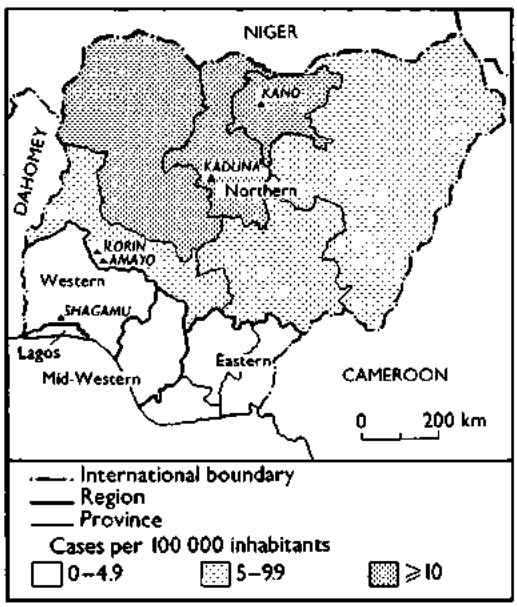


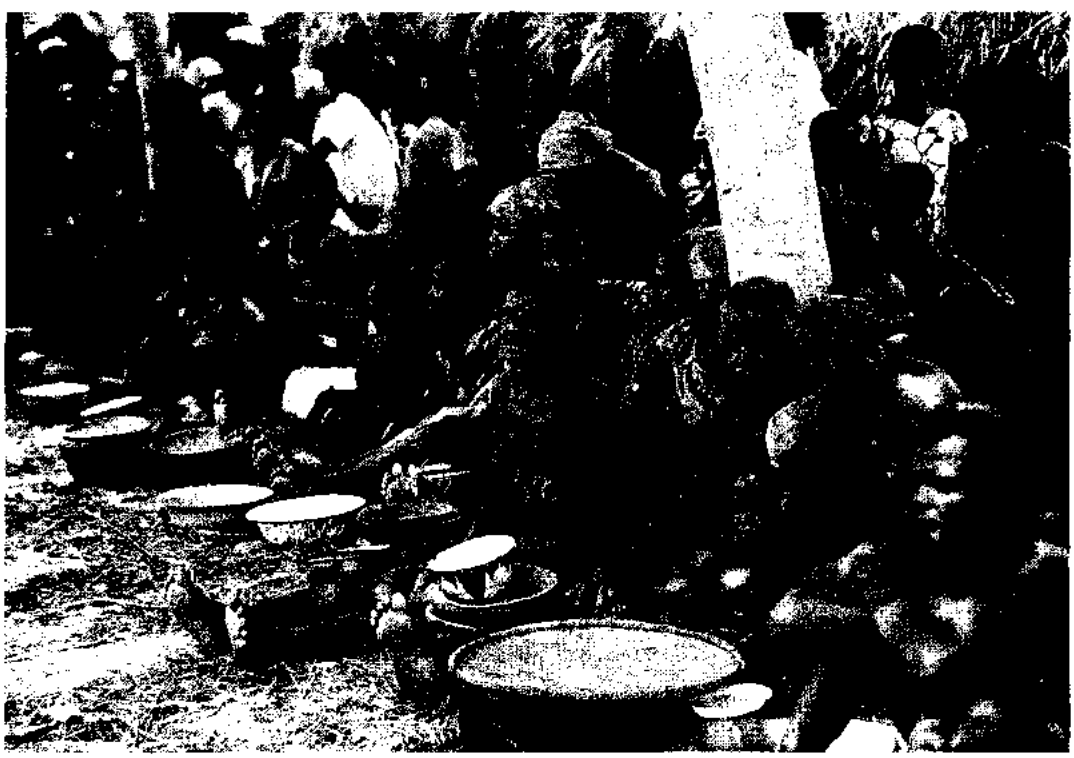
Fig. 17.5. Nigeria: smallpox incidence by administrative region and province, 1967. Early in 1967, Nigeria was made up of 4 regions and the federal capital territory of Lagos. The map also shows the provincial subdivisions in the Northern and Eastern Regions.

Table 17.10. Nigeria: number of cases of and deaths from smallpox, and case-fatality rate, in Kano Infectious Diseases Hospital, by age, 1967–1970

Age group (years)	Number of cases	Number of deaths	Case-fatality rate (%)
<1	69	15	22
1–4	189	28	15
5–14	204	18	9
15–24	418	35	8
25–44	199	29	14
≥45	11	4	36
Total	1 090	129	12

The responsibility for outbreak control was left to local health authorities, to which the government continued to issue lanolinated vaccine despite advice to the contrary by CDC staff.

In the Eastern Region, smallpox was eliminated with surprising rapidity. Mass vaccination in the north of that region, in which cases were concentrated, concluded in June 1967, simultaneously with the occurrence of the last known smallpox cases. In July, the Eastern Region having declared itself the independent Republic of Biafra, fighting between the Nigerian and Biafran armies began along its borders. The vaccination campaign decreased in intensity but did not stop immediately, and for many months vaccine continued to be transferred from Nigerian to Biafran health authorities during cease-fire periods arranged for this purpose. By the end of 1967, however, vaccination had ceased, and in 1968 widespread famine developed in Biafra, accompanied by epidemics of measles with high case-fatality rates. In October, the government of Biafra appealed for help and the International Committee of the Red Cross (ICRC) and the World Council of Churches responded with technical assistance and provided measles and smallpox vaccines, the latter coming from WHO stocks in Geneva. A vaccination campaign began again on 27 December 1968, organized by Dr A. E. Ifekwunigwe, a senior lecturer in paediatrics at the university in Enugu, Dr Nicole Grasset of the Institut Pasteur (Paris) and Dr A. T. C. Bourke, consultant to the ICRC. Despite serious shortages of petrol and staggering problems of transport and communication, 11 teams succeeded during the following year in giving an average of 100 000 smallpox vaccinations and 3500 measles vaccinations each week. Suspected cases of smallpox were investigated and specimens sent to Geneva for examination by WHO reference laboratories, but none contained smallpox virus.



ICRC

Plate 17.10. The secession of the Eastern Region of Nigeria and the civil war that ensued resulted in extensive famine throughout that area. Despite formidable problems and great personal danger, national and international staff undertook extensive smallpox and measles vaccination campaigns, with special attention to refugees in camps.

Meanwhile, by the beginning of May 1967, a pilot project in Lagos had been completed during which 1 million persons were vaccinated against smallpox; in February, the Western Region began its programme and in July more than 750 000 were vaccinated in Ibadan, the capital. Assessment showed that 90.8% of the population had been vaccinated. In the Northern Region, however, problems in reaching agreement about the conduct of the programme delayed its start until July. The vaccination campaign began in the western part of the region, in which the reported smallpox incidence was highest, and moved progressively eastwards, achieving substantially higher levels of coverage than in other parts of the country. The better coverage was achieved as a result of the edict of tribal leaders that people accept vaccination or be fined if they refused. As one programme officer commented: "In the south, a health education programme had to reach all the people to convince them to participate in a health activity, whereas in the north, a health educator only had to convince the emirs."

By the end of 1967, some 9.5 million smallpox vaccinations had been performed in Nigeria. A monthly mimeographed "Nigerian Smallpox Eradication–Measles Control Surveillance Report," which first appeared in April of that year, informed health staff throughout the country about the efforts being made. The number of cases reported in 1967 (4753) differed little from the 1966 figure (4953), most of the cases being reported during the first half of the year, primarily from the Northern Region.

Although the national programme had proceeded at a slower pace than planned, it was remarkable that so much progress had been made in a country engaged in full-scale civil war. There were problems in the delivery of supplies by air and sea, serious impediments to travel, shortages of petrol and other supplies and considerable personal risk to the teams working near the areas bordering on Biafra. Imagination, persistence and courage were required of national staff and CDC advisers alike: Dr Ademola and Dr Emmanuel A. Smith, the national programme director; Dr J. I. Adetosoye, Dr I. S. Mebitaghan and Dr P. O. Adeoye, Nigerian directors of programmes in the west, mid-west and north, respectively; and their CDC counterparts, Dr Margaret Grigsby (succeeded by Mr Lloyd Wade), Mr Warren Jones (succeeded by Mr Paul Bond) and Dr Deane Hutchins (succeeded by Mr Robert Hogan). The age distribution of cases of smallpox for which ages were recorded closely resembled that of the general population (Table 17.11), suggesting that where outbreaks occurred, primarily in rural areas, immunity was low throughout the population.

Problems in northern Nigeria continued to be substantially greater than in other regions, partly because of its size, the lack of roads and the relative paucity of health facilities, and partly because many of the senior administrative and technical staff, including mechanics, had been Ibos from the Eastern Region who had fled with the onset of war. Only 3 CDC technical staff had originally been assigned to assist, but in April 1968 their number was increased to 6 and the CDC regional office equipment specialist was transferred to Kaduna to train new mechanics in the repair and maintenance of some 60 vehicles and jet injectors. Operations were further complicated, however, by the government's decision to divide the region into 6 states, a move which required many modifications in the programme, including the reassignment of supervisors and field personnel, the restructuring of the reporting system, and changes in the budget and payment systems.

As 1968 advanced, the programme in Nigeria became fully established and during the year almost 24 million persons were vaccinated against smallpox by 60 mobile teams. In the Northern Region, assessment teams, visiting areas 7–14 days after the population had been vaccinated, usually found coverage levels of 95% or higher. For assessment elsewhere, the authorities decided to use the less satisfactory method of comparing the number of vaccinations performed with the population census figure. Although the personnel of the Western Region pro-

Table 17.11. Nigeria: number and percentage distribution of cases of smallpox by age and percentage distribution of general population by age, 1967–1968

Age group (years)	Cases		Percentage distribution of general population
	Number	%	
<1	44	3	18
1–4	231	14	
5–14	394	25	26
15–44	808	51	56
≥45	119	7	
Total	1596	100	100

Vaccine Production in Nigeria

From 1967 onwards, both CDC and WHO provided support to a government vaccine production laboratory at Yaba, near Lagos, in the hope that it might be able to manufacture sufficient high-quality freeze-dried vaccine to meet the needs of Nigeria and perhaps of other countries in western Africa. A CDC virologist, Mr Nathaniel Rothstein, was appointed to the laboratory in 1967 and, later, a WHO expert in vaccine production, Mr Ronald C. Kent, was assigned there and remained until 1976. Nigerian laboratory staff, assisted by WHO fellowships, received training in the United Kingdom, and the necessary laboratory equipment was provided by WHO. Batches of freeze-dried vaccine began to be produced in 1968 but the vaccine did not meet international standards until 1974, and then only briefly. Frequent transfers of technical personnel and management problems hampered work throughout this period. Nevertheless, the vaccine was routinely distributed for use in health centres, the vaccination teams using vaccine supplied by the USA. After 1973, the laboratory supplied all the vaccine required in Nigeria.

gramme regularly estimated the coverage to be 90% or greater, later surveys showed levels of 80% in towns of more than 5000 inhabitants and levels as low as 45–65% in the villages.

In September 1968, with the introduction of the regional "eradication–escalation" programme, efforts were made in Nigeria to improve the reporting system, which was complex and functioning poorly, some reports being delayed for weeks or even months—if they were sent at all. The system required the responsible village heads to report suspected cases to a district superintendent, and although some complied, many did not. The district superintendent, in turn, was expected to inform the superintendent for health, who was supposed to institute control measures and to forward his report to an area medical officer, who in turn reported to the regional government. Such outbreak control measures as were undertaken were largely ineffective, since the lanolinated vaccine continued to be distributed to the local health authorities. In the hope of improving reporting, efforts were made to persuade teachers, missionaries, foreign volunteers and others to report cases by recording the details on stamped addressed postcards, which had been duly supplied. In practice, however, this activity had little effect.

Although the epidemiological observations in eastern Nigeria had generated the "eradication–escalation" strategy, Nigerian staff and their CDC counterparts decided not to divert resources to this undertaking. As they assessed the situation, surveillance in northern Nigeria, in which virtually all cases were then occurring, could be established only with difficulty and over time because health centres were few, experienced personnel were lacking and the population was widely dispersed. In view of the continuing war, it was uncertain whether vaccination teams would have access to many areas in the future. Because the mass vaccination campaign was progressing well, with high levels of coverage, it seemed to the personnel concerned that the most prudent course would be to complete the campaign as rapidly as possible. That being accomplished, resources could be diverted to the investigation and containment of outbreaks. Limited surveillance activities were begun, however, towards the end of 1968, using short-term CDC epidemiologists in areas in which mass vaccination had been completed. At that time cases were found to be occurring in small outbreaks primarily among semi-nomadic Fulani herders. Having no special allegiance to the principal tribal leaders, these groups had largely been missed by the vaccination teams and by assessment teams as well (WHO/SE/68.5, Pifer & Adeoye).

The mass vaccination campaign continued to progress rapidly, concluding in the autumn of 1969. Meanwhile, the number of reported cases of smallpox declined sharply, only 5–16 cases being recorded each month from March to the end of July 1969. After July, no further

Northern Nigeria: the Role of Traditional Leaders

In northern Nigeria, strong traditional tribal leadership both helped and hindered programme implementation. One adviser recalled his surprise when attending the first mass vaccination campaign in a town to find 6000 persons already in a line at 6 o'clock in the morning. As the day progressed, he proposed to the chief that a vaccination team should move to the market area to begin work there. The chief forbade this, indicating that if all vaccinations were performed in front of him, everyone would comply, but if he were not present at the vaccination assembly point, people would report they had been vaccinated when they had not. Vaccination in this and other largely Muslim northern cities continued until long after dark, as women were not allowed to leave their homes until nightfall.

On the negative side were such problems as those encountered during the investigation of the outbreaks in 1970 in and around Amayo. A village chief, when questioned about rumours of smallpox cases, denied all knowledge of them until, during the course of interrogation, his granddaughter emerged from the house with evident smallpox lesions. Because of fear that he would be deposed from his chieftaincy if it were found that he had been hiding cases, he had suppressed information about the outbreaks.

cases were detected that year although an average of 10 rumours were investigated each month (WHO/SE/71.30, Foege). Transmission appeared to have been interrupted and, with the last cases occurring in Dahomey in September 1969, national and CDC staff scheduled a celebration for the end of March 1970 to mark the eradication of smallpox from western and central Africa. On 21 March, just as the staff were preparing to depart for the celebration, a 14-year-old girl was admitted to the infectious diseases hospital in Kaduna (Fig. 17.6) with unmistakable smallpox (*Wkly epidem. rec.*, 1970b). She had fallen ill shortly after arriving from the town of Amayo (population, 1400), Kwara State, some 400 kilometres away. The outbreak was discovered almost simultaneously by a state senior health superintendent. Intensive house-to-house vaccination and search for cases revealed 48 additional cases in the town (WHO/SE/71.30, Foege) and 12 other cases in neighbouring villages, the first cases in the outbreak having occurred in October 1969. Further investigation revealed that smallpox transmission had persisted in the area since early 1969, primarily in communities of up to 300 persons, the cases being hidden by their families from the health authorities. The search was extended to Ilorin, the capital of Kwara State (population, 300 000), only 11 kilometres away. Nine additional cases were found—the last on 22 April 1970.

Vaccination in Kwara State had been conducted between December 1968 and July 1969. However, the reassignment of personnel, which accompanied the division of the Northern Region into states, had left Kwara with fewer resources than other states, and the supervision of the programme had been poor. Teams had concentrated their efforts in the major villages and towns, but even there coverage was poor because villagers resisted vaccination. During assessment, it had been

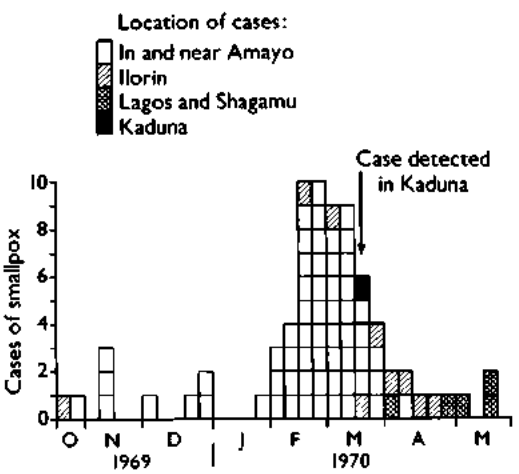


Fig. 17.6. Nigeria: number of reported cases of smallpox, by week of onset and by area, October 1969–May 1970.

found that coverage was only 70% in rural areas and 60% in the town of Ilorin; a repeat campaign had therefore been conducted in the course of which 97 000 additional vaccinations had been performed. Despite this effort, a survey in April 1970 showed that only 77% of the population had vaccination scars; in some peripheral areas of the city, the proportion was only 35%. Following the discovery of the outbreak in April 1970, a repeat house-to-house vaccination campaign was conducted, and road-blocks were established around the city to vaccinate any person who entered or left. Subsequently, special teams conducted village-by-village searches and vaccinated the inhabitants of the surrounding districts; special district search teams continued work during the following 12 months. The last known case in the area, however, occurred during the second week of April, 3 weeks after containment operations had begun.

Just as the outbreaks in the Amayo Ilorin area began to come under control, a more alarming discovery was made: 2 cases had occurred in Lagos, 150 kilometres to the south, the patients having become ill during April. Three further cases, with onset of illness in May, were discovered in Shagamu, a town to the north of Lagos. The source of infection in both outbreaks was suspected to be Ilorin, but this could not be confirmed. Intensive search and vaccination were extended in ever-widening areas around these 2 foci but no further cases were found.

The occurrence of new, widely scattered outbreaks in Nigeria was profoundly disturbing to staff throughout western and central Africa, since the cases were discovered more than 6 months after it had been thought that transmission had been interrupted and more than a year after the intensified surveillance scheme had been launched. Optimism and complacency were quickly replaced by doubt and a redoubled surveillance effort. No celebrations were in fact held until more than a year later. Although the cases in Shagamu proved to be the last, the intensified search that their presence had stimulated gave grounds for confidence that transmission had indeed been interrupted.

Dahomey and Togo

In 1967, Dahomey (population, 2.5 million) and Togo (population, 1.8 million), former colonies of France lying on the Bight of Benin between Nigeria and Ghana, were impoverished and politically unstable. Together, they cover an area between 250 and 500 kilometres from east to west and 650 kilometres from north to south. In both countries, the population was concentrated in the south. Travel from one to the other and to neighbouring countries was unrestricted and frequent because the presence of tribal groups extended across national borders. In contrast to most of the former French colonies in Africa, traditional tribal leadership remained strong and the civil governments were comparatively weak and unstable. Togo experienced 2 *coups d'état* in the 4 years immediately preceding the smallpox eradication–measles control programme; and Dahomey 6 *coups d'état* between 1960 and 1970, its first decade of independence.

Preventive medical services in both countries had all but ceased to function by 1967 because of political upheaval and lack of funds. Dahomey had had a reasonably effective mobile endemic diseases control service, which had functioned like its counterparts in other former French colonies. As recently as 1965, it had had a complement of 237 staff, operating from headquarters posts in the southern, central and northern parts of the country. The number of vaccinations given each year had been equivalent to 20–25% of the population. The activities of the service had, however, gradually diminished, and by 1967 little field work was being done. Togo had also had a mobile endemic diseases control service, which was less well supported and had effectively been disbanded in 1964–1965. The number of vaccinations performed and the type of vaccine used are not recorded.

In both countries, substantial numbers of smallpox cases were reported every year (Table 17.12), primarily from southern areas. There, as in parts of western Nigeria, resistance to vaccination had been widespread, especially in the more rural areas. The resistance was attributed to the cult worship of a smallpox fetish (see Plate 17.11) called Vodu-Sakpate, or Sopona, the major earth god of the Fon tribe. Hereditary fetish priests (*féticheurs*), who were thought by the people to have the power to prevent or to induce the disease, had traditionally performed variolation by the inoculation of pulverized scabs on the forehead, at the base of the nose or on the underside of the wrist (Glokpor, 1970). Customarily, large numbers of persons were

variolated in an affected village some 3–4 weeks after the onset of illness in the first case, in a ceremony which was said to "free the patient" of illness. For the *fétcheurs*, there were economic disincentives to cooperate in vaccination campaigns, since they were customarily given all the possessions of a patient who died of smallpox. Concern about the problem was reinforced by information that a vaccination team in Dahomey had been killed by fetish worshippers in the early 1960s.

Table 17.12. Dahomey and Togo: number of reported cases of smallpox, 1962–1969

Year	Number of cases	
	Dahomey	Togo
1962	132	571
1963	249	285
1964	703	34
1965	168	13
1966	490	201
1967	815	332
1968	367	784
1969	58	83

In Dahomey, personnel from the endemic diseases control service were again employed for a mass vaccination campaign, which commenced simultaneously in April 1967 in the northern, central and southern zones of the country. At the beginning, progress was discouragingly slow, since by government decision smallpox vaccine and measles vaccine were given by separate teams. Ultimately, however, the practice was changed and each team gave both kinds of vaccine, which resulted in a considerable improvement in programme efficiency and a reduction in cost. Better progress was also made when it was realized that tribal chiefs, especially in the southern areas, were more influential than the civil authorities. Accordingly, meetings began to be arranged with tribal authorities to explain the programme's goals and method of operation and to discourage variolation.

In August 1967, soon after the programme had begun, a special study of a small outbreak revealed quite a different epidemiological picture of smallpox in this area from that which had been anticipated (Henderson & Yekpe, 1969), a finding which contributed to

WHO / P. PITTET

Plate 17.11. The practice of variolation and resistance to visits by vaccination teams were both associated with fetish worship. At a celebration in Dahomey, a priestess dances in front of the smallpox fetish until she goes into a trance.

the formulation of the 1968 "eradication-escalation" strategy. The investigation began 10 weeks after the occurrence of the first case, but only 28 cases were found in the village of 300 inhabitants, despite the fact that only 15% of the children and 54% of the total population had vaccination scars. Surprisingly, the outbreak had terminated spontaneously, notwithstanding the many remaining susceptible persons. The study, which was conducted by Dr Ralph Henderson and Dr Maximilien Yekpe, chief of the southern sector of the endemic diseases control service, showed, moreover, that the patients were geographically clustered within the village itself despite the frequent movement of the population throughout the village. These observations reinforced the belief that smallpox in Africa spread slowly and that transmission occurred primarily as a result of intimate personal contact in households and rarely through casual contact in market-places or elsewhere. Given this pattern of spread, outbreak control was clearly more feasible than had been expected.

Assessment of the vaccination programme in Dahomey during 1967 revealed that only 28% of the population were being vaccinated by the teams and that the more remote, less accessible villages and hamlets were being missed; in some of these, smallpox outbreaks occurred after the teams had left the area. To complement the work of mobile teams who vaccinated only at assembly points, a group of 12 young health workers, called "*les douze*," was recruited, trained and given motor cycles. They worked in areas in which coverage was poor, performing house-to-house searches and vaccinating, by means of bifurcated needles, all children under 5 years of age and anybody without a vaccination scar (Yekpe, 1970).

The programme in Togo likewise got off to a slow start in 1967. The vaccination teams consisted of staff from a yaws control programme, who had continued to receive their pay but had not worked for more than 2 years. They were unenthusiastic about performing the requisite field work and made a poor showing until threatened with suspension. For political reasons, the vaccination campaign began in the north but, after a *coup d'état* and a change of government, it shifted to the south, where most cases were being reported and where villagers were both resistant to vaccination and suspicious of the government teams. The problems encountered may be illustrated by the description of an outbreak investigation conducted in November by the CDC advisers, Dr Bernard Challenor and Mr Andrew Agle. On checking a rumour of smallpox cases in a village whose inhabitants had been vaccinated twice, in January 1967 and again in October of that year, they found 8 patients, 7 of whom were hidden in the bush. The director of the medical zone, who was disturbed by these observations, decided to obtain help from the police and to take village chiefs into custody until the inhabitants of their villages had all been vaccinated. As in most areas in which police or military force was used, the result was even less satisfactory than before, since chiefs and villagers fled the area or fought with the police. That approach was soon abandoned.

Despite all the difficulties, 605 000 vaccinations were recorded in Togo in 1967 and 702 000 in Dahomey, which approximated to the projected targets. In that year the number of cases reached 815 in Dahomey and 332 in Togo, an incidence in each country which was among the highest in the world.

During the course of 1968, both countries significantly improved their reporting systems and gradually the proportion of people vaccinated in each area increased. Programme staff in both countries enlisted the help of personnel in health clinics, other health workers, foreign volunteers and tribal authorities to report cases. In south-eastern Togo, 15 health workers, comparable to "*les douze*" in Dahomey, were assigned to visit each house monthly in designated problem areas to vaccinate residents and to detect cases. In both countries, surveillance systems gradually improved and by late 1968 were well established, effective national programme leadership being provided by Dr G. F. Glokpor, Chief of the Division of Epidemiology in the Ministry of Health in Togo, and by Dr Yekpe in Dahomey. The number of vaccinations in 1968 rose to 990 000 in Dahomey but remained almost at the same level as in 1967 in Togo. In 1968, the number of reported cases decreased to 367 in Dahomey but rose to 784 in Togo—mainly owing to more complete notification.

The continuing high incidence of smallpox in Togo and reports that the entire population of villages had fled from the teams led to two studies in January 1969, one to determine what role fetish worship played in resistance to vaccination and what could be done about it, and the other to ascertain overall levels of

Table 17.13. Togo: levels of smallpox immunity by age, January 1969

Age group (years)	Persons examined				
	Total	With vaccination scar	With pockmarks	Total with pockmarks or vaccination scar	Percentage immune
<1	57	18	2	20	35
1–4	266	201	6	207	78
5–14	265	236	2	238	90
15–44	455	368	60	428	94
⩾45	119	96	16	112	94
Total	1 162	919	86	1 005	86

vaccinial immunity. Mr Gordon Robbins, the health education adviser from the CDC regional office in Lagos, conducted the fetishism study (Robbins, 1970). He discovered that the resistance to vaccination had less to do with fetish practices and attitudes than with the concern of villagers about government teams in general, many of which were then engaged in tax collection and military conscription. As he learned, many of the *féticheurs* themselves, as well as their families, had been vaccinated. To measure overall levels of immunity, a national cluster sample survey was conducted. The survey showed that immunity was surprisingly high in all age groups, except among infants under 1 year of age (Table 17.13). From these findings, it seemed unlikely that smallpox transmission could persist for long, especially with the greatly strengthened systems for case detection and containment then operating. Indeed, the last case in Togo occurred in May and the last in Dahomey in September.

Observations made during the surveillance programme in Togo during 1969 are of interest (WHO/SE/70.21, Glokpor & Agle). In that year 45 outbreaks were reported, of which 17 were notified by the routine report-

CENTRE CULTUREL AMÉRICAIN, COTONOU

Plate 17.12. Residents of the principal urban areas in Dahomey were vaccinated during mass campaigns conducted between May and July 1967.

Table 17.14. Togo: number of cases of smallpox by month, 1969

	Number of cases												
	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
Number of cases reported:													
Routine notifications	6	4	4	1	2	0	1	1	1	0	0	1	21
Other notifications	2	3	2	21	6	1	2	0	26	1	0	0	64
Number of suspected cases found during investigation	47	13	6	59	26	15	12	3	30	3	0	1	215
Number of cases of confirmed smallpox	11	9	2	53	8	0	0	0	0	0	0	0	83

ing centres, comprising 190 dispensaries and polyclinics and 15 hospitals; 9 were found by smallpox teams in the field; and 19 were reported by other sources. The other sources included a radio-club president, village chiefs, a civil administrator, a social worker, an employee of the social welfare bureau, and members of malaria control spraying teams. Twenty-five of the 45 reported outbreaks were confirmed to be smallpox; two-thirds of the outbreaks and more than half the cases were in generally remote and isolated villages of less than 200 inhabitants. In these places vaccination coverage was usually found to be lower than 50%.

The differences between the number of smallpox cases routinely notified and the number actually confirmed are shown in Table 17.14. If routine notification data had been accepted, 21 cases would have been recorded in 1969, the pattern of occurrence suggesting that smallpox had been transmitted continuously throughout the year. During the investigation of these 21 cases, as well as that of 64 other suspected cases reported by other sources, a total of 215 cases of fever with rash were identified, of which only 83 were smallpox. All occurred between January and May.

Of the 61 cases discovered in Togo during April and May 1969, all but 2 were in riverine areas, difficult of access, in the south-east near the border with Dahomey. There, resistance to vaccination had been the greatest and, despite two intensive vaccination campaigns, only 60% of the population had vaccination scars (Table 17.15). Early in April, programme staff were notified of suspected cases by a health centre and, on investigation, they discovered 8 outbreaks with a total of 47 cases. The first of the cases had occurred 2 months before but neither these nor subsequent cases had been reported by the responsible health worker, who, as was later discovered, had vacated his post in January. With transmission apparently close to being interrupted, the President of Togo requested the army to form a *cordon sanitaire* around the areas, and police accompanied teams to lend authority to the effort; markets were closed and public gatherings forbidden. Personnel drawn from other regions vaccinated 45 420 persons in April, a figure which, by September, had grown to 248 854. The last 2 cases in this series of outbreaks occurred towards the end of April, less than 3 weeks after the initial discovery of cases. A survey in September showed that vaccinial immunity had increased from 60% to 93%.

Togo's last 2 outbreaks, numbering 6 cases in all, were discovered in May 1969 in isolated but reasonably well vaccinated fishing villages near the border with Dahomey. These were apparently the last cases of a major epidemic which had occurred throughout the area late in the preceding year.

Table 17.15. Amecho-Vogan area, Togo: vaccinial immunity by age before and after April 1969, as ascertained by survey in September 1969

Age group (years)	Persons examined			
	Total	With vaccination scars (%)	Vaccinated before April 1969 (%)	Vaccinated after April 1969 (%)
<5	490	421 (86)	77 (16)	344 (70)
≥5	1 610	1 526 (95)	1 181 (73)	345 (21)
Total	2 100	1 947 (93)	1 258 (60)	689 (33)

Table 17.16. Togo: number and percentage distribution of cases of smallpox by age, 1967–1969[a]

Age group (years)	1967 cases		1968 cases		1969 cases	
	Number	%	Number	%	Number	%
<1	9	4	30	5	10	12
1–4	39	18	136	23	18	22
5–14	59	27	169	28	14	17
15–44	95	44	229	38	31	38
⩾45	13	6	31	5	8	10
Total	215	99	595	100	81	100

[a] Details are not available for 308 other cases reported during this period.

Transmission appeared to have been interrupted in Dahomey in January 1969, but in July an infant from Dahomey was diagnosed as a smallpox patient in a dispensary in Togo near the border. Teams from the two countries converged on the area in a coordinated search and vaccination operation on both sides of the border. In all, 55 further cases occurred in Dahomey over the next 2 months but in September 1969 the last case was detected. Until March 1970 (see the section on Nigeria, above) this was thought to have been the last case in western and central Africa.

Programme staff in Togo collected data regarding the age distribution of most smallpox cases occurring between 1967 and 1969; these are presented in Table 17.16. It is of interest that each year 40–50% of all cases occurred among persons aged 15 years and over. This finding reflected the occurrence of the disease in isolated rural villages which experienced smallpox only infrequently and whose inhabitants were poorly vaccinated.

Although programmes in Dahomey and Togo had only limited resources, they began to function reasonably well after little more than a year, and only 18 months later transmission was interrupted. Resistance to vaccination in the southern areas of the countries proved to be a problem, although variolation, associated with fetish practices, was observed only once during the course of the programme.

Mali, Niger and Upper Volta

The third of the 7 groups of countries are 3 inland states, which extend over 2.8 million square kilometres in the central part of western Africa—Mali (population in 1967, 5.3 million), Niger (population, 3.9 million), and Upper Volta (population, 4.8 million). Topographically, the area encompassed by these countries consists of desert in the north, giving way to the semi-desert areas of the Sahel and then to savanna in the south. In Upper Volta the population was evenly dispersed throughout the country, but in Mali and Niger the northern areas were very sparsely populated, virtually all of Mali's population living in the southern half of the country and 90% of Niger's being concentrated along the western and central segments of the Niger river, near the country's southern border, in a belt less than 250 kilometres wide. Thus, although both Mali and Niger were far larger than Upper Volta, the areas with a significant concentration of population in these countries were only slightly greater than in Upper Volta. As in most parts of western and central Africa, roads were few and communications difficult.

The majority of the population were sedentary agriculturalists living in villages of fewer than 1000 inhabitants. Large numbers of pastoral nomads, however, were to be found in all 3 countries, being especially numerous in Mali and Niger. They were predominantly Tuareg and Peuhl tribal people, who moved along well-defined routes seeking pasturage for their animals. During the May–October rainy season, the nomads worked on farms or congregated in pasture areas, but during the October–April dry season, they migrated over great distances. During this period, smallpox spread extensively.

OCCGE had its headquarters in Upper Volta and the country's endemic diseases control service, directed by a French military medical officer, was perhaps the best supported and most effective of such services in western Africa in 1967. In Niger, a similar service existed, but its performance was much less satisfactory. In Mali, which had ceased to receive financial support from France, the multi-purpose teams no longer functioned, having been replaced in 1962 by 2 mobile smallpox vaccination teams.

In these countries, in which health services were traditionally provided by mobile teams, there was both interest in and a structure for a large-scale combined smallpox and measles vaccination campaign. As has been described earlier, Upper Volta had, in fact, completed a national measles vaccination campaign in 1962. However, the assessment of vaccination coverage and surveillance were unknown

practices, and government officials considered them unnecessary. Moreover, views differed within each of the countries as to whether separate teams should conduct the measles and smallpox vaccination campaigns or whether they should, in some manner, be incorporated into the scope of work of multi-purpose teams. Because of these problems, there were delays in the signing of programme agreements, although all the programmes became operational by April 1967. In the end, none provided for ongoing assessment of vaccination coverage; surveillance activities, although originally intended to be conducted by national teams, became, by default, the responsibility of CDC advisers.

In Mali, a special smallpox vaccination campaign had been in progress since December 1962 with 2 teams, each composed of 15 persons, administering freeze-dried smallpox vaccine provided by the USSR and yellow fever vaccine produced in Senegal. Mali was handicapped by a lack of trained personnel, transport and petrol and requested assistance from WHO, which began to be provided in 1964; a WHO medical officer was assigned to the programme in December 1965.

A WHO team which assessed the Mali programme in February 1965 described the prospects for eradication there as "bleak" (World Health Organization, 1965b). In the campaign, vaccinators were expected to average 140 vaccinations a day, but even this modest target was not being met. At that rate of work, the WHO team estimated that it would take at least 8–10 years to complete one round of vaccination. Such vehicles as were available were old and frequently out of order, and refrigerators did not function. The vaccine was stored at ambient temperatures of up to 50 °C, which caused it to deteriorate and the take rates to decline as a result. The vaccination campaign did not improve materially during 1965–1966, but the number of reported cases decreased significantly, reaching, in 1966, the lowest total ever recorded in Mali (Table 17.17).

With the offer of AID assistance, government health officials in Mali decided to reconstitute the multi-purpose mobile teams, 8 such teams being created to administer yellow fever vaccine, as well as smallpox and measles vaccine, and to examine and treat patients for onchocerciasis, trypanosomiasis and leprosy. The problems involved in drawing up plans and in training teams for this more complex set of activities delayed the launching of the programme. Further delays resulted from the government's insistence that each trip the CDC advisers (Dr Pascal Imperato and Mr Jay Friedman) made outside the capital should be authorized weeks in advance. Although this requirement applied to all foreign advisers at the time, it was apparent that this policy would seriously handicap the necessary training of staff and all but preclude the establishment of surveillance and containment measures. The problem was compounded by a lack of collaboration between the smallpox eradication adviser assigned by WHO and the CDC staff, which resulted in the government's receiving contradictory advice. In view of the many constraints and frustrations, senior CDC smallpox eradication staff proposed suspending assistance until the problems could be sorted

Table 17.17. Mali, Niger and Upper Volta: numbers of reported cases of smallpox and vaccinations performed, 1962–1969

Year	Mali (population, 1965: 5 105 000)		Niger (population, 1965: 3 736 000)		Upper Volta (population, 1965: 4 648 000)	
	Number of cases	Number of vaccinations	Number of cases	Number of vaccinations	Number of cases	Number of vaccinations[a]
1962	1 521	234 000	1 038	321 000	1 550	..
1963	1 096	302 000	445	536 000	341	..
1964	343	530 000	330	587 000	8	..
1965	626	501 000	463	318 000	14	..
1966	281	457 000	1 023	301 000	69	..
1967	293	1 043 000	1 187	1 610 000	195	2 040 000
1968	134	1 472 000	678	1 166 000	100	2 208 000
1969	1	1 193 000	28	936 000	0	1 338 000

[a] .. = data not recorded.

out. When confronted with this possibility, the government decided to give the advisers full freedom to travel; a new Chief Medical Officer, Dr Ousmane Sow, was appointed; and the WHO smallpox eradication officer completed his assignment and returned home. The campaign proceeded to gain rapid momentum. The complex logistics and problems of conducting a vaccination campaign in areas such as Mali have been described by Dr Imperato in his book, *A Wind in Africa* (Imperato, 1975).

The teams began work in areas in the eastern part of the country, in which most cases of smallpox were then being reported. The cases were mainly among nomads and in remote rural areas (Imperato et al., 1972), a distribution attributed to the great distances separating the vaccination assembly points established during the 1962–1966 campaign. Early surveys in the more accessible areas revealed that 93% of the farmers, but only 54% of the nomads, had vaccination scars. In some areas, the inhabitants of entire villages, far from the assembly points, remained unvaccinated, as were many young children and elderly persons, who could not easily walk or be carried over long distances. Assembly points continued to be used, as in the earlier campaign, but they were more numerous, requiring the villagers to travel less far.

In April 1967, the CDC advisers began to investigate some of the outbreaks. The first were in east-central Mali, in which mass vaccination had been completed in 1965 but, as was discovered, less than half the population had a vaccination scar. Smallpox transmission, nevertheless, was not rapid, even in the season of highest incidence. In one outbreak, for example, only 71 cases were found to have occurred over a 4-month period (Imperato, 1970). As the programme moved towards the border with Upper Volta, the teams began to encounter a large number of persons who refused vaccination and found that many women and children were hidden when the teams arrived. Vaccination continued throughout the east-central area, 521 000 people being vaccinated over a 2-month period beginning in October 1967. Although programme staff had expected to find epidemic smallpox occurring widely throughout the country, only 293 cases were discovered during 1967, most of which were in areas bordering on Upper Volta, in which a mass vaccination campaign was in progress. Of the

WHO / CHI-VAIPH

Plate 17.13. Mass vaccination in Mali, using jet injectors.

total, 145 cases occurred in a cluster of 5 villages whose aggregate population was only 3700. Variolation was responsible for some of the cases—the only occasion on which variolation was observed in Mali.

Following the mass campaign in the endemic border areas, 2 further outbreaks, of 12 and 28 cases, were discovered in March 1968 among unvaccinated children who had been hidden from the teams (Imperato et al., 1973). Repeat vaccination in the respective villages quickly terminated the outbreaks, and for 6 months no further cases were found or notified in the entire country. It appeared that smallpox transmission in Mali had been interrupted by the time the vaccination campaign was little more than a quarter of the way towards completion.

On 6 November 1968, however, programme staff in Mali received a telegram from Upper Volta informing them that the first case in an outbreak near the border had come from a village in Mali. The Upper Volta outbreak—the last in that country—had begun in May 1968 and although 6 months had elapsed since the first case had entered Upper Volta from Mali, programme staff from the two countries agreed that a joint search should be undertaken. This began on 14 November. The village from which the initial case had come was 10 kilometres from a road and could be reached only by a narrow footpath through a mountainous rocky area. On arrival, the teams discovered that the village consisted of 8 widely separated groups of huts with a population of about 1350 people. During the vaccination campaign, which had concluded 1 year previously, the villagers had been directed to visit an assembly point 10 kilometres away, but few had done so. An outbreak had begun in late 1967 and spread progressively from one of these groups of huts to another.

Despite the fact that this was then Mali's only known focus of smallpox, the containment measures were surprisingly incomplete: only 541 villagers (40%) were vaccinated and only 16% of them were found to have vaccination scars. Pockmarks indicative of recent smallpox were observed in 65 of the 541 people examined, the last person to contract the disease having become ill in October 1968, a month before the team's arrival.

Only 1 further case was discovered in Mali, in February 1969; it occurred in a migrant tribal group believed to have been infected in Niger. This was the last of 9 known outbreaks, comprising a total of 370 cases, which had originated among migrant Tuaregs and Peuhl nomads between 1967 and 1968, and accounting for more than three-fourths of all cases recorded in Mali (Sow, 1970).

In Upper Volta, smallpox vaccination had been a routine activity of the mobile multipurpose teams, and the director wanted to continue this practice. He believed, correctly, that smallpox was then substantially under control and saw no reason to mount a special effort, since he did not consider eradication of the disease to be achievable. However, he decided to create special teams to administer measles vaccine, much as had been done in the 1962 campaign.

Smallpox incidence in Upper Volta had diminished greatly after 1962, as it had in Mali. Because there were comparatively few cases and responsibility for the smallpox vaccination campaign had been assumed by the endemic diseases control service, the CDC advisers, Dr Christopher D'Amanda and Mr William White, devoted substantial time to the improvement of reporting and the investigation and containment of outbreaks. In 1967 they discovered 195 cases, mainly along a north–south route used by pastoral nomads. In 1968, however, the epidemiological pattern changed. Only 100 cases were found, all of them in small villages near the border with Mali or Niger (D'Amanda, 1970). One outbreak of 19 cases in a village only 3 kilometres from the border with Niger led to a joint vaccination campaign by teams from Niger and Upper Volta. In October 1968, the last outbreak in Upper Volta was discovered by one of the multi-purpose teams in a village of 650 persons situated in a rocky mountainous area near the border with Mali. Forty cases had occurred between May and October, the first being infected in Mali; only 2 patients remained with active disease. Thorough vaccination in this and neighbouring villages quickly stopped transmission.

The concentration of cases along the frontier areas, in which health dispensaries were the most scarce, led to changes in the programme strategy in 1969. The schedule of the multi-purpose teams was altered to achieve a thorough coverage of the frontier areas, and the 604 mobile and established health units, as well as members of mobile teams giving leprosy treatment, were asked to supply weekly reports. The new system elicited many additional rumours of smallpox cases, but

transmission had ceased by then and no importations were detected.

For Niger, smallpox was a much greater problem than for Mali or Upper Volta. In all, 1023 cases were recorded in Niger in 1966 and 1187 in 1967. Until 1967, the numbers of smallpox vaccinations given by mobile teams, in proportion to population, were comparable to those in Mali, but the campaign in Niger had not achieved effective smallpox control. In part, the failure could be attributed to the high ambient temperature and the inactivation over time of improperly stored freeze-dried vaccine. This was apparent from studies conducted in early 1967 which showed primary take rates of only 20–25%. Another contributory factor was Niger's proximity to northern Nigeria. Most of the population lived within 250 kilometres of the Nigerian border, and many travellers crossed it. Mali and Upper Volta, in contrast, were at a considerable distance from the heavily endemic coastal areas of neighbouring countries.

Of special concern to the CDC advisers, Dr Donald Moore and Mr Anthony Masso, as well as to the national programme staff, were the nomads, estimated to number about 530 000. They travelled widely throughout Niger and to neighbouring countries and were, therefore, considered to constitute a special risk in the spread of smallpox. Moreover, they were said to practise variolation when outbreaks did occur, thereby amplifying the outbreaks and increasing dissemination.

The vaccination campaign, utilizing teams devoted solely to giving smallpox and measles vaccine, began well and, by the end of 1967, 1.61 million people—equivalent to 41% of the population—had been vaccinated. A component of the programme during its first year was a special campaign aimed at vaccinating nomads, some 150 000 of whom gathered annually in a pasturage area 600 kilometres from the capital. Although the strategy was sensible, it proved to be a far more difficult endeavour than had been expected when the rains turned the few dry roads into a quagmire which could scarcely be traversed even with 4-wheel-drive vehicles. A sand storm ripped the tents and scattered the camping equipment, and the nomads sought to evade the

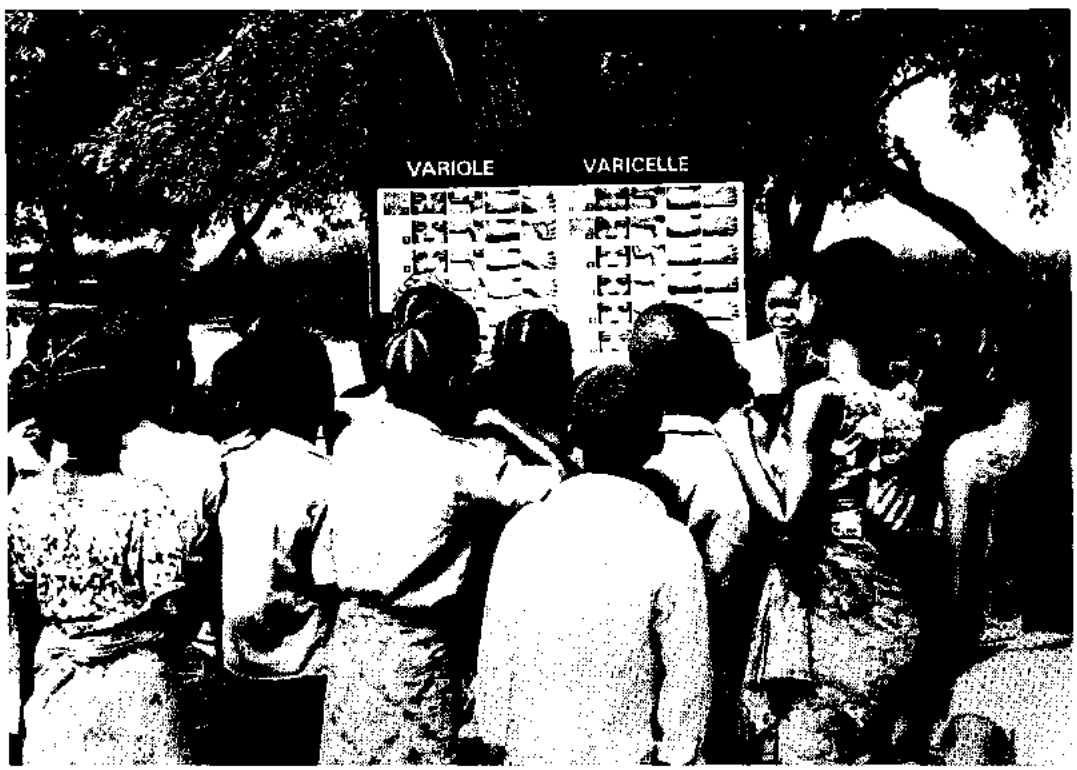


Plate 17.14. In Niger, a health worker uses the WHO diagnostic wall chart to explain the difference between smallpox and chickenpox, an important educational activity in the surveillance phase of the programme.

teams, fearing that they were also engaged in tax collection. Ultimately, as was revealed by assessment, only 45% of the population were vaccinated.

In 1967 and the early months of 1968, some outbreaks in Niger were investigated and containment vaccinations performed, but the principal effort was directed to the difficult logistics of the vaccination campaign. During the first 6 months of 1968, an additional 725 000 persons were vaccinated, following which—and coincidentally with the beginning of the seasonal rains—smallpox incidence declined sharply and did not increase again. Only 24 cases were recorded during the last 6 months of 1968 and another 28 cases in 1969. Although they were not fully documented, all the cases in 1969 are believed to have resulted from importations from Nigeria.

Despite the concern of programme staff, nomads in Niger—unlike those in Mali and Upper Volta—were found to play only a minor role in transmitting smallpox from place to place, even in the more densely populated areas. In the vast but sparsely populated northern regions of Niger, in which an estimated 150 000 nomads lived, only 1 case was discovered. That smallpox did not spread through this area was welcome but unexpected, and was probably partly due to a comparatively high level of immunity induced by vaccination as well as variolation (Masso, 1970). In a survey conducted in 1969, 38% of the nomads examined were found to have vaccination scars, but an additional 29% had the scars of variolation. Evidence of past variolation was frequently observed in different parts of Niger, and although the practice was originally believed by health staff to be important in sustaining transmission, only a single instance of recent variolation was observed—in October 1967 in a village near the Nigerian border.

The transmission of smallpox in Mali, Niger and Upper Volta was interrupted more rapidly than had been foreseen, but the problems of logistics and vaccination proved greater than expected. In Mali and Upper Volta, previous vaccination campaigns had been successful in sharply reducing the incidence of smallpox, and in less than 2 years—in November 1968— transmission was interrupted in both countries. In Niger, smallpox incidence was high at the outset of the programme, but the vaccination campaign progressed rapidly and transmission was interrupted at about the same time as in the other countries.

Guinea and Sierra Leone

The fourth of the 7 groups of countries to be discussed consists of 2 neighbouring coastal countries, Guinea and Sierra Leone. Programmes in both countries began in December 1967, nearly 12 months after the regional programme had started. As has been noted earlier in this chapter, the reason for the delay was that the CDC staff wanted to phase in activities over a 2-year period. When this decision was made, the fact was not recognized that cycles of epidemic smallpox had recurred in these countries at intervals of 10–12 years. Major epidemics had occurred in Sierra Leone in 1956–1958, and in Guinea in 1955–1957, although in the latter country nearly 3000 cases occurred only 5 years later, in 1962. In both countries, epidemic smallpox recurred early in 1967 (Table 17.18). Sierra Leone (population, 2.7 million) recorded 1697 cases and Guinea (population, 3.7 million) 1530 cases, giving incidence rates for that year which were among the highest in the world. In aggregate, the total number of cases represented nearly a 10-fold increase in incidence over 1966.

The launching of both campaigns in December 1967 coincided with the advent of the dry season—the season of highest incidence—and the beginning of the second year of the epidemic. Smallpox being a matter of much concern at the time, Guinea and Sierra Leone gave their full support to the programme and developed plans to complete the mass vaccination campaign within 16 and 24

Table 17.18. Guinea and Sierra Leone: number of reported cases of smallpox, 1960–1969

Year	Number of cases	
	Guinea	Sierra Leone
1960	176	12
1961	96	6
1962	2 948	78
1963	224	14
1964	320	90
1965	70	60
1966	56	293
1967	1 530	1 697
1968	330	1 143
1969	16	80

months, respectively. In the summer of 1968, case detection and outbreak containment were given special emphasis. Smallpox incidence declined rapidly, and the last cases were recorded in January 1969 in Guinea and in May 1969 in Sierra Leone. Benefiting from experience in the other countries of western and central Africa, these programmes were the best executed and the best documented. An account of the programme in Sierra Leone has been given by Dr Evelyn Cummings, the Chief Medical Officer, and Dr Donald Hopkins and Mr James Thornton of CDC, and their colleagues (Hopkins et al., 1971a, b, c). Guinea's programme has been described by Dr A. B. Alécaut, the director of the country's endemic diseases control service, and Dr Joel Breman, the CDC medical epidemiologist, and their colleagues (Alécaut et al., 1970; Breman, 1971; Breman et al., 1977a, b).

The population in both countries consisted primarily of sedentary farmers living in villages of less than 1000 inhabitants, most of which were not readily accessible by motor vehicle. The most densely populated part was the coastal area from Freetown, the capital of Sierra Leone, to Conakry, the capital of Guinea. In the more sparsely populated area comprising north-eastern Guinea and north-eastern Sierra Leone, cattle herders moved freely between the two countries. Work in the diamond mines of eastern Sierra Leone attracted many farmers during the dry season.

In 1967, neither country had a continuing special programme for smallpox vaccination. Vaccinations were performed by the established health units and, in Sierra Leone, by a mobile unit of the endemic diseases control service, which periodically conducted small-scale mass vaccination campaigns. Approximately 700 000 persons were reported to have been vaccinated each year in Guinea and 300 000 in Sierra Leone. In Guinea, freeze-dried vaccine from Switzerland and the USSR began to be used in the early 1960s. Sierra Leone, like Nigeria, employed the thermolabile lanolinated vaccine purchased from the United Kingdom or Nigeria. Surveys in Sierra Leone when the programme began revealed vaccination scars in only 26% of those under 15 years of age and in 60% of older persons. Overall, almost half the population of Sierra Leone was considered to be susceptible to smallpox. Comparable data from Guinea are not available.

Smallpox incidence began to increase in Sierra Leone in 1966 (Table 17.18); in 1967 the disease became endemic throughout the country, the eastern areas being the most affected. In Guinea, the incidence started to increase a year later, the most heavily afflicted areas being the coastal districts bordering on Sierra Leone (Fig. 17.7.). Because of the spreading epidemic, an emergency mass campaign was conducted in Conakry in February and March 1967, during which 180 000 of the city's 250 000 inhabitants were vaccinated.

In Guinea, the AID-supported vaccination campaign began in December 1967, utilizing, as supervisory personnel, senior staff of the former endemic diseases control service, which, by 1967, had ceased to function owing to a lack of vehicles and of funds for petrol and equipment. Vaccination was conducted by 8 mobile teams of 6 persons each: a team leader, 2 vaccinators, a recorder, a driver and an "advance man". The last-named visited leaders of the well-organized political party in each area and village prior to the team's arrival, in order to acquaint them with the programme and to obtain their support. To simplify the logistics of providing supplies, all teams worked together in a given region of the country, vaccinating at assembly points situated so that villagers had to walk no more than 2–3 kilometres. Local costs, which amounted to US$10 000 per annum, were covered by WHO.

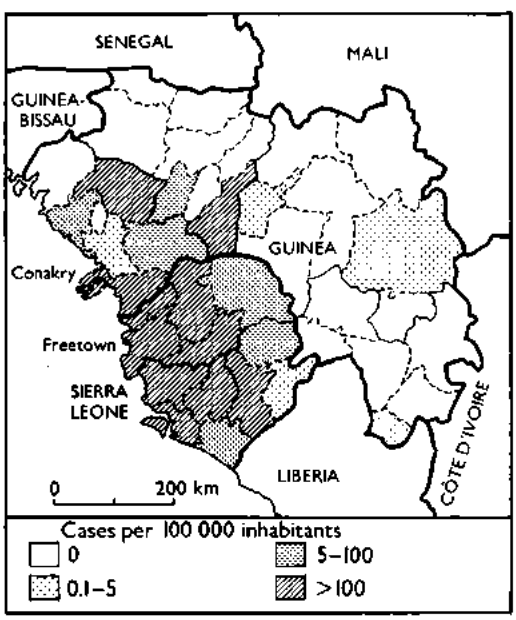


Fig. 17.7. Guinea and Sierra Leone: smallpox incidence, by province, 1967.

From the beginning, vaccination coverage in Guinea was carefully assessed. Two methods were used. The first, performed when the teams were working in the village, consisted simply in comparing the numbers vaccinated with the population census. If the numbers vaccinated seemed to be low, local party officials were asked to search for those who had been missed, and send them for vaccination. Where vaccination coverage was particularly low, a special team was assigned to conduct repeat mass vaccination and vaccine was sometimes left with regional officials, who were asked to vaccinate the people who had been missed.

The second form of assessment, conducted a week later by a senior technical officer of the programme and an assistant, utilized the modified cluster sample technique devised by Dr Ralph Henderson (Henderson et al., 1973); this required the examination of a number of persons sufficient to ensure, with 95% confidence, that the results obtained were within 10% of the true value. Although this was a more sophisticated survey method than that routinely employed in other programmes, it was well executed. As the programme progressed, it was found that the results of the two types of assessment usually corresponded well, due primarily to close supervision of teams and the availability of unusually accurate census data.

With the active cooperation of party leaders, the levels of vaccinial immunity achieved usually exceeded 80% and more often 90%. The teams themselves averaged 2000 smallpox vaccinations a day and, in addition, provided measles vaccination to all children between 6 months and 4 years of age.

From January to October 1968, the end of the rainy season, the residents of Conakry and of all districts bordering on Sierra Leone were systematically vaccinated (Fig. 17.8). These areas included most parts of the country then known to be infected with smallpox.

The investigation and containment of outbreaks began within months of the start of the mass vaccination campaign. In June 1968, a special surveillance team was assigned this responsibility and asked to make a village-by-village search for cases in high-risk areas. By then, owing to the decrease in incidence during the rainy season and the high levels of vaccinial immunity in previously infected areas, smallpox had all but disappeared. From July 1968 to the end of January 1969, only 8 outbreaks, with a total of 75 cases, were

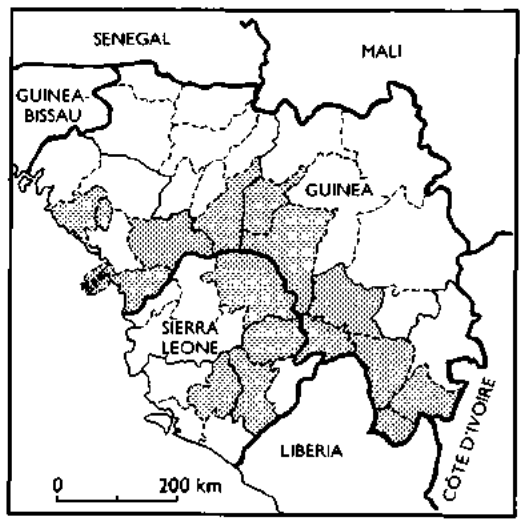


Fig. 17.8. Guinea and Sierra Leone: areas (shaded) in which mass vaccination was completed before the end of the rainy season, October 1968.

discovered, almost all in villages of less than 500 inhabitants. All were in western Guinea, near the border with Sierra Leone, and 5 of the 8 were thought to have originated in that country. In each instance, information regarding the source of infection was cabled promptly to Sierra Leone. The last known case in Guinea was reported and investigated in January 1969, though it actually occurred in December 1968.

The first phase of the systematic vaccination campaign continued until June 1969. In all, 3.1 million smallpox vaccinations were given during the 18-month period, another 2.6 million during a subsequent 2-year cycle, and a further 2 million in a third 2-year vaccination cycle. Meanwhile, weekly reports from each of the 29 regions were being received with increasing regularity. In 1968, 33% of the expected reports were received—a proportion which increased to 60% in 1969, and to 87% in 1970.

The smallpox problem in Sierra Leone differed from that in Guinea in that the disease was widespread throughout the country. The campaign, which began in January 1968, utilized the staff of the endemic diseases control service, which had previously been responsible for 43 treatment centres for yaws and trypanosomiasis. Six teams performed the vaccinations and one the assessment. The composition of the teams and their methods of work were similar to the system operating in Guinea. Priority was given to

eastern Sierra Leone, in which smallpox incidence was the highest, presumably because of a large population turnover associated with diamond mining and the migration of cattle herders. Because of the epidemics, attention was initially concentrated on vaccinating as widely and as rapidly as possible before the end of the rainy season in 1968 and the commencement of the expected seasonal increase early in 1969.

The help of tribal chiefs in the 146 chiefdoms was necessary to obtain the cooperation of villagers. Although the chiefs were generally receptive, they proved to be less effective than Guinea's political party leaders. Efforts were made to achieve a vaccination coverage of 80% or more in all areas, but assessment showed that it was usually no greater than 75%.

A few outbreaks were investigated between January and August 1968, but a concerted effort to investigate and to contain all reported outbreaks did not begin until August, when the regional "eradication escalation" activity commenced. Vaccination teams were assigned in rotation to this duty. As in Guinea and in other countries at this time, outbreak containment consisted primarily of 1–2 days of intensive vaccination in the infected village, in neighbouring villages and in nearby markets. Patients were isolated in their houses, a traditional practice in most of this part of Africa. Nearly all the cases (94.5%) in Sierra Leone occurred in villages of less than 1000 inhabitants and although containment measures were less rigorous than in the later phases of the Intensified Smallpox Eradication Programme, most outbreaks ended quickly. Studies by the programme staff showed that no secondary cases occurred in villages in which coverage was greater than 80%, and 1–9 secondary cases in those in which vaccinial immunity was less than 70%.

An unusual feature of smallpox transmission in Sierra Leone was the occurrence of outbreaks associated with special funeral ceremonies for smallpox victims. In two documented outbreaks (Hopkins et al., 1971c), cases occurred among members of secret societies who washed the corpse of the smallpox victim and among others who attended special funeral services. One of the outbreaks gave rise to 33 cases among contacts at the funeral and an additional 97 cases due to further spread; the other resulted in 10 contact cases and 2 cases due to secondary spread. While secret societies were prevalent throughout western Africa, and other such outbreaks were believed to have occurred in Sierra Leone, these were the only ones which could be documented.

From August 1968 onwards, the number of cases in Sierra Leone decreased steadily and from January to the end of April 1969, only 12 outbreaks, with a total of 80 cases, were found, all but one situated in coastal areas in which mass vaccination had not yet been conducted. On 5 April, the last case occurred, in Freetown; it was not officially reported until May and the source of infection was not discovered.

An important contribution to the success of the programme was the monthly publication of a mimeographed bulletin, *The Eradicator*, which was distributed widely to programme staff, medical officers, dispensers, civil officials, paramount chiefs and other interested persons. It reported on the programme's progress, paid tribute to effective health workers and local officials and announced the schedule of activities for the coming month. When the intensified surveillance programme began in August 1968, the bulletin served to stimulate reporting throughout the country.

Data on the age distribution of cases and case-fatality rates in Guinea and Sierra Leone

1979

Plate 17.15. Donald R. Hopkins (b. 1941), a CDC epidemiologist, served as the senior adviser to the programme in Sierra Leone. Although the incidence of smallpox in Sierra Leone was among the highest in the world in 1967, it was possible to interrupt transmission in only 16 months. Hopkins later wrote a history of smallpox, *Princes and Peasants*.

Table 17.19. Guinea and Sierra Leone: number of cases of and deaths from smallpox and case-fatality rate, by age, 1968–1969

Age group (years)	Guinea[a]			Sierra Leone[a]		
	Number of cases	Number of deaths	Case-fatality rate (%)	Number of cases	Number of deaths	Case-fatality rate (%)
<1	9	5	56	35	7	20
1–4	77	10	13	163	14	9
5–14	94	0	0	270	10	4
15–44	116	7	6	522	70	13
⩾45	9	1	11	105	14	13
Total	305	23	7.5	1 180	131	11

[a] Data are not available for 41 cases in Guinea and 43 cases in Sierra Leone; in addition, the age distribution of 85 cases in Sierra Leone is unknown though their outcome was recorded.

were more complete than in most national programmes, and it is pertinent to include them here, since they are probably representative of the situation in other countries of the region (Table 17.19).

In proportion to population, cases were more numerous among children than adults, but there was, nevertheless, an unusually large percentage of adult cases in what were considered to be endemic countries. Most of the cases, however, occurred in rural areas, in many of which smallpox had not been present for several decades. The low levels of vaccinial immunity in these areas, coupled with the infrequency of variolation, ensured the presence of many susceptible adults when outbreaks occurred. Because of the nature of data collection, the case-fatality rates probably understate the severity of the disease. Since in most of the fatal cases of smallpox, the patients did not die until the second or third week of illness, some who were acutely ill at the time of outbreak investigation may have died later but their deaths were not recorded. An overall case-fatality rate of perhaps 10–15%, depending on the age distribution of cases, would probably be more correct.

The programmes covering the comparatively small populations of Guinea and Sierra Leone, both highly endemic at the start, are of interest because of the rapidity with which they succeeded in interrupting transmission. Guinea's last case occurred only 12 months, and Sierra Leone's only 16 months, after the inception of their respective programmes. This achievement in two countries which were so lacking in health services, transport, and communications greatly encouraged regional and global smallpox eradication programme staff and, to some extent, generated an unwarranted confidence that comparable successes could be achieved as readily in other parts of the world.

Côte d'Ivoire, Ghana and Liberia

In the adjoining countries of Côte d'Ivoire, Ghana and Liberia, smallpox had largely been brought under control by 1967; Côte d'Ivoire, in fact, had succeeded in interrupting transmission (Table 17.20). Each had achieved this status in a different manner: Côte d'Ivoire by mass vaccination, with little external assistance; Liberia through a mass vaccination campaign supported by a private voluntary organization; and Ghana by a remarkably effective programme of surveillance and containment.

Ghana is of special interest, being one of the few countries in which an effective programme of case investigation and outbreak control all but interrupted smallpox transmission despite a comparatively low level of vaccinial immunity in the population

Table 17.20. Côte d'Ivoire, Ghana and Liberia: number of reported cases of smallpox, 1961–1968

Year	Number of cases		
	Côte d'Ivoire	Ghana	Liberia
1961	4 656	70	1 116
1962	2 141	145	325
1963	282	23	88
1964	623	9	258
1965	27	7	40
1966	10	13	32
1967	2[a]	114	6
1968	0	24[b]	5

[a] Imported from Upper Volta.
[b] Imported from Togo.

and the use of a thermolabile smallpox vaccine. Ghana was the second most heavily populated country in the western and central African region (population in 1967, 8.1 million), and in the 1950s and 1960s had one of the best-organized health services and networks of all-weather roads. A moderately extensive morbidity reporting system had been established, and a compulsory mortality registration scheme covered approximately half the population. Between 500 000 and 1 million persons were vaccinated annually in hospitals, health centres and health posts and by mobile rural health service teams (originally called medical field units). The thermolabile lanolinated vaccine produced in the United Kingdom was used exclusively until 1964, when freeze-dried vaccine began to be purchased from Switzerland. However, on the basis of field observations by a WHO adviser in 1965, and outbreak investigations in 1967, it can be assumed that overall vaccinial immunity was probably not greater than 50% when the programme began. Despite this, no more than 251 cases had been notified in any year since 1953—that is, during a period when many countries in western and central Africa with smaller populations reported 1000 or more cases every year. The explanation can be found in the existence of a corps of well-trained sanitarians who took special care to keep the vaccine refrigerated, investigated all outbreaks, isolated patients in a hospital or in separate quarters, vaccinated those living in the area and recorded the daily temperature of household contacts in order to detect additional cases as early as possible. Only 7 cases of smallpox were notified in 1965 and 13 in 1966.

The mass vaccination campaign began in February 1967 in the capital, Accra, utilizing the mobile health service teams to give both smallpox and measles vaccine. At the same time, senior Ghanaian programme staff, Dr Frank Grant and Dr V. de Sario, with the CDC advisers Dr Challenor, Dr David Melchinger and Mr James Lewis worked with local sanitarians in the investigation and containment of outbreaks. In all, 17 outbreaks, with 114 cases, were found in 1967. Two of these, with a total of 21 cases, were in Accra and affected only 7 households in an area populated by immigrants from Togo; 5 others, with 27 cases, were in southern Ghana, the Accra outbreaks being the source of one of them and Nigeria another; 10 outbreaks, with 66 cases, occurred in a cluster of small villages within a few kilometres of the point where the borders of Ghana, Togo and Upper Volta meet (WHO/SE/69.8, de Sario). The last group of outbreaks occurred in a tribal area in which no cases had been seen for 6 years but in which smallpox was well recognized by its name *naba*, which means "the chief of all the other diseases". A source of infection in Togo or Upper Volta was suspected but not proved. Although the sources of infection could not be traced for all outbreaks, it is apparent that there was little endemic disease and few chains of transmission. During 1968, 24 additional cases in 6 outbreaks were discovered, all of which could be traced to importations from Togo, 2 of the outbreaks occurring very near the border, while the others were at a distance of more than 100 kilometres from it (Grant, 1970).

The mass vaccination campaign progressed steadily but more slowly than in most other countries of the region, being completed in 1970, 4 years after it had begun. Coverage levels, based on concurrent assessment, were consistently over 90%.

In Côte d'Ivoire (population in 1967, 4.9 million), smallpox had been an important problem in the early 1960s, 4656 cases having been reported in 1961. In August of that year, the government decided to embark on a special 3-year mass vaccination campaign using a freeze-dried vaccine produced in France and 5 mobile teams comprising 50 health staff. The responsibility for its execution was entrusted to the Institute of Hygiene in Abidjan and its director, Médecin-Colonel Gaston Binson. During the next 3 years, 3.6 million persons were vaccinated; a repeat 3-year campaign, lasting from 1964 to 1966, succeeded in vaccinating another 3.7 million. Smallpox incidence fell precipitously and by 1965, only 27 cases were notified, followed by 10 cases in 1966.

When assistance was provided by the USA, the government decided to undertake a third national smallpox vaccination campaign under the same leadership as before; other teams from the Ministry of Health, working independently, administered measles vaccine. The smallpox vaccination campaign differed somewhat from those in other countries in that the vaccine was administered by scarification rather than by jet injector. Dr Binson saw little virtue in speeding up the rate of vaccination by using the jet injector, since this was offset by the time-consuming process of preparing for each person vaccinated a signed

Plate 17.16. Headquarters of the national smallpox eradication programme at Abidjan, Côte d'Ivoire.

personal vaccination certificate giving the individual's name, the date of vaccination and the batch number of vaccine used. The preparation of a vaccination certificate was traditional in Côte d'Ivoire, as in many of the other francophone countries and, while most countries soon abandoned the practice or simply distributed certificates without the holder's name inscribed, the traditional approach continued to be used in Côte d'Ivoire. Assessment of coverage was not performed. In November 1969, at the conclusion of the third national mass smallpox vaccination campaign, measles vaccination teams were merged with the smallpox teams, the practice of issuing vaccination certificates was abandoned and jet injectors began to be used for both antigens.

After the regional programme had commenced, only 2 cases of smallpox were discovered in Côte d'Ivoire, in March 1967, both of which were importations from Upper Volta. The cases did not appear in the official records, however, until 2 years later; the director of the programme, proud of its accomplishments, believed that the country's record should not be blemished by 2 cases for which he did not feel responsible.

Liberia (population in 1967, 1.3 million), which abutted on Côte d'Ivoire in the west, reported more than 1000 cases in 1961, and the following year began a smallpox vaccination campaign. It was directed by a religious organization called Brother's Brother, which undertook mass vaccination throughout the accessible, populated areas (Bryant, 1968). Over a 5-month period, some 775 000 vaccinations were reported to have been given, using jet injectors of a different type from those subsequently employed by CDC, and a freeze-dried vaccine, which was diluted approximately 15-fold owing to a lack of supplies. Neither vaccination take rates nor coverage was assessed.

After the 1-year mass campaign, WHO provided an adviser, Arita, and enough freeze-dried vaccine to permit a more systematic programme which utilized undiluted vaccine administered by scarification. That this was needed became apparent when Arita found that only 60–70% of persons had had successful primary vaccinations when vaccinated in accordance with the procedure used by the Brother's Brother group. Progress in the WHO-supported programme was slow, but smallpox incidence continued to fall. Although the number of reported smallpox cases had averaged more than 1000 per annum from 1958 to 1962, only 325 cases were reported after the first mass campaign in 1962. The figure dropped to only 40 cases by 1965, to 32 by 1966 and to 6 by 1967.

The AID-supported campaign, which began early in 1968, progressed little more satisfactorily than had the campaigns in 1962–1967. Even with 7 vaccination teams, nearly 4 years were required to complete the operation. Assessment was seldom conducted and reporting remained almost as unsatisfactory at the conclusion of the programme as at the beginning. Nevertheless, a system which had notified hundreds of cases in previous years reported only 5 cases in 1968, all of which occurred during the first 3 months of that year. Nothing is known of these cases, since no reports of cases were investigated until April 1968. Some—perhaps all—may have been erroneously diagnosed, or they may have been importations. No further cases of smallpox were discovered by vaccination teams as they advanced systematically across the country, but in 1970 they did detect the first cases of human monkeypox outside Zaire (see Chapter 29).

The Gambia, Mauritania and Senegal

The Gambia, Mauritania and Senegal, 3 contiguous countries comprising the westernmost part of the region, recorded no cases of smallpox after 1966 (Table 17.21). The

Table 17.21. Gambia, Mauritania, Senegal: number of reported cases of smallpox, 1961–1967

Year	Number of cases		
	Gambia	Mauritania	Senegal
1961	12	12	201
1962	4	40	232
1963	52	0	231
1964	6	0	2
1965	6	2	2
1966	3	76	0
1967	0	0	0

cessation of reported smallpox that year followed many years of effective control measures, especially in Senegal, which accounted for 70% of the area's population (in 1967) of 5.3 million and which was economically the most developed. The Gambia, a strip of land 16 kilometres wide and 320 kilometres long, entirely surrounded, except for the coastal section, by Senegal, had a population of 438 000, which moved freely back and forth across the border. Not surprisingly, its experience with smallpox reflected that of Senegal. Mauritania, although 6 times larger than Senegal, was mostly desert. Because its predominantly nomadic population of 1.2 million was widely dispersed throughout the country, the transmission of smallpox was not easily sustained. After 1962, Mauritania reported 78 cases of smallpox—2 in 1965 and 76 in 1966. Government reports, however, note that the 1966 cases, all in a confined area, had never been confirmed by a physician and, in retrospect, chickenpox was thought to have been a more probable diagnosis.

In Senegal, the endemic diseases control service had been in operation for many years and had a personnel of 292 in 1967. With a reasonably extensive network of all-weather roads, the multi-purpose mobile teams were able to move comparatively easily throughout the country. Vaccinations, equivalent in number to about 20% of the population, were administered annually. Since the early 1960s, a good-quality freeze-dried vaccine produced in France had been used, a factor which undoubtedly contributed to the interruption of smallpox transmission. No surveys were performed either before or during the programme to assess the level of vaccinial immunity, but it was believed to be reasonably high. For the AID-supported programme, the government decided that the supplies and equipment provided should be utilized by its mobile teams, which endeavoured to visit all villages once every 3 years. During the first 3 years of the programme, 2.6 million smallpox vaccinations were performed. No cases of smallpox were discovered.

In the Gambia, some 50 000–75 000 smallpox vaccinations had been administered annually at health centres and dispensaries, using lanolinated vaccine produced in Nigeria. Few of the health units, however, had refrigeration equipment; supplies of vaccine were distributed monthly and kept in wet cotton until used. Mass vaccination had been conducted only once during the preceding decade—in a localized area in 1963, when an outbreak of 52 cases occurred. The proportion of successful vaccinations is unknown, but it was probably not high, as the method of storage would not have preserved the thermolabile vaccine for more than a few days. Despite the presumably low levels of vaccinial immunity and the fact that 10% of the population was migratory, few cases of smallpox were recorded, the immune barrier provided by Senegal undoubtedly playing an important role in protecting the Gambia.

With assistance provided by the USA for smallpox and measles vaccination, 3 mobile teams were created, each consisting of 2 vaccinators, a tally clerk and a driver; a health superintendent, Mr Kebba A. M. Sanneh, supervised field activities. The mass vaccination campaign began in June 1967 and was completed in 10 months (167 working days), during which 350 000 people were vaccinated against smallpox and 81 000 against measles, an average of 2580 vaccinations a day. This far surpassed the expected average of 1500 vaccinations a day (see box). The continuing programme of maintenance vaccination was no less successful. Concurrent assessment regularly showed coverage rates of more than 90%, which were sufficiently high to interrupt measles transmission for more than 2 years. No cases of smallpox were discovered after the programme had begun.

Mauritania presented a set of problems quite different from those encountered either in the Gambia or in Senegal. Like Senegal and other former French colonies, Mauritania had had an endemic diseases control service, which consisted of 7 mobile teams, each composed of 5 health workers. About 125 000 people were being vaccinated annually against smallpox with a freeze-dried vaccine produced in France. However, in 1962, most senior staff of the service left Mauritania, and thereafter team activities diminished sharply,

Factors in the Success of the Programme in the Gambia

In a detailed paper (unpublished), the Gambian field supervisor, Mr Kebba A. M. Sanneh, enumerated the factors which he considered to be of importance in the success of the programme.

Training: The field supervisor was trained first and actively participated in training the teams, all of whose members (vaccinators, recorders and drivers) were trained together. This created a special team spirit. Included in the training were 5 stand-by vaccinators who could replace any who became ill. After several days of classroom training, a 3-day field exercise was conducted in a large village to work out practical problems.

Publicity and scheduling: Before the programme began, it was given wide publicity through the local press and radio, and through letters to all medical and health personnel, as well as to Divisional Commissioners, and through them to district chiefs. In each district, the field supervisor met each *seyfo* (chief) to discuss the programme and to obtain a list of all villages and hamlets. The *seyfo* was asked to inform each *alkalo* (village head) of the programme and assign a "badge messenger" (a type of policeman) to work with the teams. One day before the teams vaccinated in a village (the population of as many as 20 villages were vaccinated each day), a team member met the *alkalo* and requested him to ask each family head to bring his family to the vaccination assembly point. The field supervisor was given wide latitude in planning the programme, but once a village had been informed that the teams would be present on the following day, every effort was made to reach it even if this meant working for 12 hours or more.

Support of teams: Team morale was enhanced by support given to them by headquarters staff and other government personnel. If transport was sent on a Sunday to obtain vaccine and petrol, these would be supplied, although Sunday was not a normal working day. In addition, teams were paid promptly whenever they returned to the capital. They were given priority at ferries by Marine Department personnel, and priority in vehicle repair by the Public Works Department. The CDC advisers, Dr Thomas Drake and Mr Robert Helmholz, gave help wherever this was required, sharing with the teams the hardships of field living conditions.

Local customs: Public support was actively sought but no compulsion was used and no attempt was made, at any time, to foreshorten the traditional greetings required in the Gambia before any matter could be taken up for discussion. Where teams encountered the initiation ceremonies for circumcision, which necessitated the isolation of the boys and girls concerned from others in the village, the boys were vaccinated "in the bush", and the girls were vaccinated privately in a compound.

With good support from local government and villagers alike, the morale and enthusiasm of the teams remained high, permitting a programme scheduled to last 260 working days to be completed in 167 days, with an independently assessed rate of coverage of more than 90%.

only penicillin and aspirin being distributed during the period 1962–1967.

With the provision of assistance from the USA, it was decided to reconstitute the endemic diseases control service and to add smallpox and measles vaccination to its tasks. For ease of supervision it was decided that the teams would work in two separate groups, progressing from one region to the next, rather than assigning one team to each of 6 regions. However, in 1967, following the outbreak of hostilities between Egypt and Israel, Mauritania severed diplomatic relations with the USA. The United States adviser left the country and field activities ceased after only one week, not to be resumed until 1969.

In March 1968, Dr Mayer, the WHO intercountry smallpox adviser for western Africa, visited Mauritania and, with government officials, developed a plan of operations which provided for the assignment of a WHO medical officer and an operations officer, as well as a vehicle, some items of equipment

and funds to cover local costs. The USA agreed to provide vaccines and other supplies and equipment, using OCCGE as an intermediary. The arrangement was similar to that which was devised to support the programme in the Congo.

At government insistence, two basic changes were made in the original plan: BCG vaccine (provided by UNICEF) would also be administered, and the teams would work simultaneously in 6 rather than 2 regions. In a country of 1.2 million square kilometres with few, poorly maintained roads, the dispersal of teams created difficulties in communication as well as in supervision and supply. Air transport was of little help since scheduled weekly flights served only a few of the larger towns and were frequently cancelled owing to the breakdown of equipment and to sandstorms.

Dr Mayer moved from Liberia to Mauritania in May 1968 and shortly thereafter conducted a scar survey among village children in the north of the country. Vaccinial immunity was found to be poor: among the children up to 14 years old only 45% had vaccination scars and these were almost all in the 5–14-year-olds. After 7 months of preparation, pilot field activities were resumed in January 1969, and full operations commenced in April. The programme progressed slowly, owing to difficulties in supervision and supply and to mechanical problems with vehicles. In 1969, 426 000 smallpox vaccinations were given and about one-fourth this number of measles and BCG vaccinations. In 1970, the number of vaccinations decreased by half and remained at about this level until June 1976, when the programme came to an end. However, no cases of smallpox were detected after 1966.

Although the need for smallpox vaccination in the 3 countries was questionable, since all of them had remained free of smallpox after 1966, the campaigns also provided measles vaccination and the vaccinators, in their systematic travels through the countries, were able to ensure that no foci of smallpox had been missed.

The OCEAC Countries: Cameroon, Central African Republic, Chad, the Congo and Gabon

Of the last group of countries to be dealt with in this chapter, all were members of OCEAC, then directed by Médecin-Colonel Labusquière. The 5 countries (population in 1967, 13.7 million) comprised an area of almost 3 million square kilometres, which, until 1960, had been known as French Equatorial Africa. In the provision of health services, each country relied primarily on the well-established multi-purpose mobile teams of the endemic diseases control service, directed by French medical advisers who were usually military officers. The programmes in these countries all followed the same pattern, which had been agreed on in the meetings of OCEAC.

The method of operation has been described by Dr J. M. Roux, the Chief Medical Officer of Chad (Roux, 1970). A typical team consisted of 12 male nurses, 2 drivers with vehicles and 2 labourers. They administered smallpox, BCG and yellow fever vaccines; examined each person for leprosy and trypanosomiasis as well as other common endemic diseases; conducted simple routine tests on specimens of blood, faeces and urine; and prescribed appropriate treatment. For every individual examined, a special certificate documenting each procedure was prepared and retained by the person concerned. Two or three years were required for the teams to visit all parts of the country.

A freeze-dried smallpox vaccine of good quality, produced in France, began to be used

J. S. FRIEDMAN

Plate 17.17. A health worker in Gabon repairs a jet injector. Jet injectors made it possible to vaccinate large numbers of people very quickly, but they frequently malfunctioned and their daily maintenance was essential.

Table 17.22. OCEAC countries: number of reported cases of smallpox, 1961–1969

Year	Number of cases				
	Cameroon	Central African Republic	Chad	Congo	Gabon
1961	1 145	0	502	23	0
1962	743	57	769	1 254	1
1963	135	3	10	1 476	111
1964	88	0	5	198	49
1965	28	0	73	89	1
1966	2	0	0	0	0
1967	119	0	86	0	0
1968	37	0	5	0	0
1969	3	0	0	0	0

in the early 1960s, and soon thereafter the number of reported cases of smallpox declined sharply, only 2 cases being recorded in the 5 countries in 1966 (Table 17.22).

In the initial planning for the regional programme, CDC staff had not been fully aware of the scope and extent of activities already being carried out in these countries, and had envisaged the need to create special teams for measles and smallpox vaccination such as had been done during the earlier AID-supported measles vaccination campaigns. However, OCEAC and government officials decided to incorporate the new vaccination activities into the work of the multi-purpose mobile teams, and to utilize the vehicles and equipment to strengthen existing efforts. Although this was advantageous to the execution of the vaccination campaign, the prescribed operations provided for neither concurrent assessment of the work by sample surveys nor a surveillance team to investigate suspected cases of smallpox.

OCEAC officials decided that the provision of separate assessment teams would be too costly and that it was basically unnecessary, since assessment in the OCEAC countries was conventionally done by the vaccination teams, who compared the numbers vaccinated with the estimated population in the area served. In most countries, such assessments proved misleading, partly because of inaccurate census data, but the OCEAC programmes were generally well conducted, and independent assessments, when performed, usually revealed that at least 80% and often more than 90% of the population had vaccination scars. By late 1969 and early 1970, the total numbers of smallpox vaccinations administered in each country during the course of the regional programme were almost equivalent to or exceeded the estimated population.

The investigation of suspected cases was generally undertaken by the CDC advisers, with assistance from local officials. After 1966, all smallpox cases in the OCEAC countries were discovered in Cameroon and Chad, in areas bordering on Nigeria. The outbreaks in Chad were traced to importations from Nigeria, as were most of those in Cameroon.

In Cameroon, during 1967–1969, 21 outbreaks, with 159 cases, were detected among tribal peoples who lived in widely scattered settlements in the rugged Mandara mountains adjacent to Nigeria. The villagers frequently crossed into Nigeria and some, in fact, maintained houses in both countries in order to escape taxes. Many villagers resisted vaccination, and because of the difficult terrain, the multi-purpose teams had not vaccinated extensively throughout the region. When surveys showed that 40% of the inhabitants had never been vaccinated, special smallpox vaccination campaigns were conducted in 1967 throughout the area, primarily in the crowded market-places. By March 1968, the last of the large outbreaks had been contained (Delas, 1970). Over the next year, however, 9 additional outbreaks of 1–7 cases occurred among visitors to Nigeria, then still heavily endemic and in which neither vaccination nor surveillance had yet begun.

The outbreaks in Chad occurred among villagers living on thousands of floating islands on Lake Chad, a shallow lake some 250 kilometres long and 25–100 kilometres wide. The islands, inhabited by fishermen, consisted of matted networks of papyrus reeds and other weeds, which often drifted for miles over the surface of the lake. Cases were reported from the area by a missionary physician in June 1967—the first cases known to have occurred in the lake area for more than 2 years. To investigate the outbreak, Dr Bernard Lourie, the CDC adviser, chartered an aeroplane with pontoons, and using a medical service boat and 4-wheel-drive vehicles, he and Chadian staff eventually identified more than 100 cases, not all of which were officially reported. The first had occurred in April among fishermen returning from Nigeria. Smallpox then spread from one small village to another in an area in which only 20–30% of the population bore the scars of vaccination. A special vaccination campaign was conducted in markets and villages

throughout the area. The floating islands presented a special problem, because when pressure was exerted on the pedal of the jet injectors, they tended to sink through the surface. The difficulty was solved by laying mats on the island. In all, some 80 000 people were vaccinated in an area thought to have a population of about 150 000. Transmission was interrupted within a matter of weeks, although importations resulted in 5 further cases in 1968.

Throughout the OCEAC countries, roads were few, the distances were great and communications were limited. Secessionist groups, who were active throughout the central and northern parts of Chad, compounded the problems there and taxed the skills of the able director of the mobile disease control service, Dr Pierre Ziegler. Rebel groups, in fact, ambushed a team, killing a labouret, wounding a driver and setting fire to one of the vehicles. Efforts to contact the secessionists to ensure safe passage proved futile, since the different groups acted independently and assurances provided by one leader did not obligate others. Accordingly, vaccination in these areas had to be restricted to the major towns and cities which had military garrisons. Neither surveillance nor vaccination was possible in rural areas of the north, but the population was sparse there, and smallpox transmission did not persist as it did under similar conditions in the Ethiopian Ogaden in 1975–1976.

CONCLUSIONS

The elimination of smallpox in 1970 – little more than 3 years after the inception of the Intensified Smallpox Eradication Programme—from the vast region of western and central Africa provided enormous encouragement to the remaining endemic countries. The fact that many countries of the region were among the world's poorest, with the least developed infrastructures of health, transport and communication, increased confidence that global eradication could eventually be accomplished. The valuable early insights into the epidemiology of smallpox and the methods for its control were no less important. Subsequently, the experience acquired by both national and CDC staff was to prove invaluable when many of them served with programmes in other parts of the world.

The regional programme was also important in that the USA provided sufficient support to make eradication feasible in this vast region; WHO did not then have resources of this magnitude available for programmes in other endemic areas. The fact that CDC staff assumed full responsibility for technical assistance permitted WHO Headquarters staff to direct their efforts and attention elsewhere. Indeed, in view of the formidable administrative problems that WHO encountered in implementing smallpox eradication programmes in other countries of Africa, it is problematic whether eradication in Africa could have been achieved without this support. At the same time, WHO's own modest but vital contribution to many of the countries by meeting the "local costs" of items such as petrol and vehicle maintenance and repair must be acknowledged.

This programme is identified with the first effort to implement, as national policy, a strategy which accorded priority to the discovery of outbreaks and their containment, even if these activities meant some compromise in the pace of execution of the mass vaccination campaign. An important change of emphasis in the global strategy took place as a result, and, in supporting this change, WHO staff frequently cited the successful experience of the regional programme. In retrospect, however, when the relative contributions made by mass vaccination and surveillance–containment ("eradication–escalation") are weighed, the importance of surveillance–containment to the western and central Africa programme itself is less certain. When such measures were actually implemented late in 1968, the mass vaccination campaign had already reached some 60 million persons, more than half the population of the region, and a much higher proportion of those in the known endemic areas, to which the campaign had given priority. Endemic smallpox then remained in only a few of the countries, and where surveillance teams actively sought to discover and to contain outbreaks—as in Dahomey, Guinea, Sierra Leone and Togo—smallpox transmission had practically ceased, the remaining outbreaks being small and in isolated rural areas. The strategy was not employed in northern Nigeria, then the principal focus of smallpox. There, programme staff undertook to contain outbreaks only in areas in which the mass vaccination campaign had been completed.

Thus although the rapid demise of smallpox in western and central Africa was impressive, and the success of the programme attributed to the new strategy, the well-executed mass vaccination campaign using freeze-dried vaccine probably played the more decisive role.

In this region, as well as in most of Africa south of the Sahara, the interruption of smallpox transmission proved to be more straightforward and less difficult than in Indonesia and the Indian subcontinent. In contrast to the Asian countries, the population density in Africa was lower, population movement was less, vaccination was usually more readily accepted, and many villagers, by tradition, isolated smallpox patients. When the comparatively simple surveillance–containment methods used in Africa were employed in Asia, the results proved disappointing. In Bangladesh, India and Pakistan, in particular, whose populations had generally higher levels of vaccinial immunity than those of African countries, surveillance and containment measures failed to make a significant impact on the disease until the methods were substantially modified and strengthened.

As had been hoped, the programme in western and central Africa served to strengthen the foundation for disease reporting and preventive services in all the countries concerned, but with only 5 years of operational experience the endeavours could not be fully institutionalized. Thus, in 1976, when it became necessary to certify that eradication had been achieved, special programmes had to be organized to permit certification (see Chapter 25).

Subsequent chapters describe eradication programmes in other countries of Africa, which, with some notable exceptions, consisted largely of mass vaccination campaigns but which succeeded in eliminating smallpox with surprising rapidity.

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CHAPTER 18

ZAIRE AND SUDAN

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INTRODUCTION

Eradication programmes in a group of contiguous countries of western and west-central Africa began in 1967 and 1968, with support primarily from the USA and technical assistance provided by the United States Communicable Disease Center. East of this area lay two of Africa's largest countries—Zaire and the Sudan (Fig. 18.1). (Zaire was named the Democratic Republic of the Congo from 1960 to 1971, but its present name is used throughout this chapter for convenience.) Their combined population in 1967 amounted to only about 33 million, but their total area (approximately 4.85 million square kilometres) was equivalent to that of the whole of Europe, excluding the European part of the USSR. Transport and communications in both countries were poor and the terrain was difficult. Zaire was in WHO's African Region and the Sudan in its Eastern Mediterranean Region.

In the African Region, Zaire strategically had the highest priority for the allocation of WHO resources. Smallpox was endemic throughout the country; in 1967, it accounted for one-third of the total number of cases reported in the countries of central, eastern and southern Africa. Indeed, of all the African countries, only Ethiopia was to record more cases after the Intensified Smallpox Eradication Programme began. Vaccinial immunity was low throughout the country. Along its lengthy western, northern and southern borders lay 5 countries which had interrupted smallpox transmission or seemed close to doing so—Angola, the Central African Re-

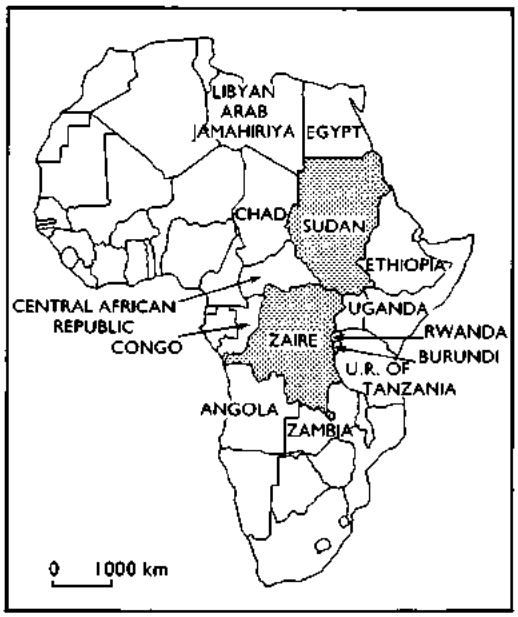

Fig. 18.1. Sudan and Zaire and adjacent countries.

public, the Congo, the Sudan and Zambia. In all, these 5 countries reported 686 cases in 1965 and only 66 in 1966. Because of the frequent movement of travellers across the Zairian border, importations of smallpox were inevitable. When they occurred, the detection and control of the outbreaks, especially in border areas, were problematic owing to the paucity of health services and the difficulties of travel and communication.

The status of smallpox in the Sudan was entirely different. A mass vaccination campaign using freeze-dried vaccine had been conducted throughout the central and northern parts of the country between 1961 and 1963. The Sudan reported no cases at all in 1963, 1964 and 1966; in 1965, 69 cases occurred as a result of importations. However, in the country's 3 southern provinces, which had a population of about 2.5 million, government health services were restricted to the larger towns because of a protracted, devastating civil war. Thus, the status of smallpox in the extensive rural areas of the south could not be known with certainty. Even so, there was hope that the disease might not be present. No cases were being detected in the towns, no imported cases from this area were being found in adjacent countries despite the considerable numbers of migrants and travellers, and reports reaching WHO from revolutionary groups in the south indicated that no known cases of smallpox were occurring. Moreover, the area was sparsely populated, making the sustained transmission of smallpox difficult.

Agreements to undertake eradication programmes were signed by the Zairian government in November 1966 and by the Sudanese government in April 1967. In both countries, the plans called for the administration of BCG (antituberculosis) vaccine to children and adolescents at the same time as the whole population was being vaccinated against smallpox. It was the first time a national programme had been attempted which incorporated the simultaneous administration of the two vaccines. The concept seemed sensible but, logistically, there were problems because the BCG vaccine had to be administered intradermally. In Zaire, inoculation was performed at collecting points, and there it eventually proved feasible to use the jet injectors for both smallpox and BCG vaccination. In the Sudan, however, the jet injectors were not practical because in many areas the population was not accustomed to assembling at collecting points. Smallpox vaccine was therefore administered with the bifurcated needle by vaccinators moving from house to house, but the administration of BCG vaccine by syringe and needle was too cumbersome to permit this procedure. Accordingly, programme staff endeavoured, without great success, to gather the children at assembly points.

In addition to the problems inherent in administering two vaccines rather than one, both programmes faced other difficulties, including those of conducting campaigns in large areas in which civil disorder was prevalent. Moreover, in Zaire, trained manpower in all sectors of government was scarce, communication facilities were few, the network of roads was limited and in poor repair, and travel through dense tropical rain forests was difficult. However, a highly effective vaccination campaign began to take shape there in 1968, and by July 1971 a carefully assessed systematic programme had been completed throughout the country during which smallpox vaccine was given to more than 24 million persons and BCG vaccine to more than 11 million. The last recorded case of smallpox appears to have occurred in June 1971.

Because of the lack of trained staff and the size of the country, organized surveillance was not developed until after the completion

of the vaccination campaign, and thus few outbreaks were investigated. However, an excellent surveillance system subsequently evolved, which served to strengthen the existing health structure and to confirm the absence of smallpox. Between 1970 and 1986, more than 400 cases of monkeypox, a disease clinically resembling smallpox (see Chapter 29), were eventually discovered.

The hope that the Sudan would remain free of smallpox was shattered late in 1968, when increasing numbers of cases began to be detected among persons living in the war-stricken south near the Ethiopian border and among migrant agricultural labourers from that area. Meanwhile, a mass vaccination campaign had been initiated in provinces in the central part of the country, but it was disrupted by the occurrence of cholera in 1970–1971. Although the investigation and containment of all suspected cases in a country believed to be smallpox-free were considered by WHO to be of high priority, no programme for the purpose was developed. Smallpox spread across the country in 1970 and 1971. In only 2 African countries that were free of smallpox in 1967 did endemic smallpox become re-established, and the Sudan was the first of these. Finally, in January 1972, a Sudanese medical officer took the initiative of developing a surveillance–containment programme which interrupted transmission with such unexpected rapidity that WHO consultants recruited to help to strengthen the operation arrived just as the last cases were occurring. Thereafter, Sudanese surveillance teams assisted Ethiopian staff in search activities along the border, as well as in Ethiopia itself.

ZAIRE

Background

Zaire, Africa's third largest country, is mostly low plateau (average altitude, 500 metres), comprising the central basin of the Zaire (formerly Congo) river and its tributaries. Higher plateaux surround the low plateau, rising to mountains in the east. Extending 2300 kilometres from east to west, much of the country is covered by dense tropical rain forest, giving way at higher elevations to wooded savanna and grassland. Throughout central Zaire, temperatures are uniformly high (24–27 °C), as is the humidity. In 1967, almost 90% of the inhabitants were rural dwellers, many living in clusters of 10 20 houses along roads or tracks. Of the 233 000 kilometres of roads, only 3000 kilometres were of the all-weather asphalt type. In extensive riverine tropical rain forest areas, villages could be reached only by boat or on foot. Kinshasa, the capital (then called Léopoldville), was the largest city in tropical Africa (population, about 1 million), but there were 9 other cities in Zaire with populations of 100 000 or more. Telegraphic and postal services were limited and unreliable; communication among the various tribal groups, speaking more than 200 different languages and dialects, posed a problem.

Zaire became independent in June 1960 but within a week, an army mutiny and threatened secession brought in a United Nations peace-keeping force, which remained for 4 years. A large-scale United Nations technical assistance programme was also initiated and continued in operation until 1969. With the departure of the United Nations forces, rebellion recurred throughout the north-eastern provinces and sections of those in west-central Zaire. After the autumn of 1965, the conflict gradually subsided, but security in parts of the country remained a problem for several years. During the long period of fighting, roads and bridges were destroyed or deteriorated, and the structure of the health services was greatly weakened. Not surprisingly, few persons were vaccinated against smallpox during this time.

Trained personnel throughout the country were proportionately far fewer in Zaire than in most African countries. Primary education had been made widely available during the 1950s, but few people had been educated in secondary schools or institutions of higher learning. There were, for example, no national physicians in 1960, only 88 in 1965 and only 221 in 1970.

Because of the dearth of educated national staff, United Nations and bilateral technical assistance programmes provided many of the necessary senior and middle management personnel for the government. In the health sector, there were, in 1965, 427 foreign physicians, of whom 86 were provided by WHO and 75 by Belgian and French assistance; the remainder worked primarily in mission hospitals and clinics or were under contract with the government.

To carry out a national programme with the situation as it was in 1967 represented a formidable undertaking.

Smallpox Before 1967

During the decades preceding the beginning of the programme, several thousand cases of smallpox had been recorded annually in Zaire, but, because reporting was poor, this represented only a minute fraction of the total which had occurred. The disease was prevalent throughout the year, with no seasonal fluctuations. Mass vaccination campaigns had been conducted sporadically in urban areas and in some rural districts, but vaccination, employing locally produced liquid vaccine, was frequently unsuccessful.

It is probable that both variola major and variola minor prevailed in the country at different times. However, from 1962, smallpox with a case-fatality rate of 5–15%, similar to that in western Africa, was most widely prevalent. Official reports from Zaire usually distinguished between variola major and variola minor (Table 18.1). From these data, the inference might be drawn that variola major, similar in severity to that which occurred in Asia, coexisted with variola minor. During the course of the programme, however, it became apparent that health staff usually based their reports simply on the severity of the disease. Milder cases were customarily reported as variola minor and more severe cases as variola major.

Before 1962, overall case-fatality rates were below 5%, but subsequently they ranged from 5% to 15%. Since no changes are known to have occurred in reporting practices, it is presumed that a more serious form of the disease became more widespread about this time. After 1962 there were occasional undocumented anecdotal reports of outbreaks with few or no deaths; conversely, in Kinshasa a 1961–1962 epidemic was reported in which 280 (27%) of 1021 cases died. However, in the Kinshasa outbreak almost all the cases reported (of which 70% were in children under 5 years of age) were of the more severe type, requiring hospitalization.

Whatever the cause of the higher case-fatality rate, the government authorities of the newly independent country, as well as the foreign medical officers working there, were concerned about smallpox. In 1962–1963, they held meetings with the WHO medical officer for smallpox from Geneva to plan a pilot programme in one of the provinces. It was hoped that this would be followed by a national smallpox vaccination campaign. WHO was asked to provide medical officers, vehicles and equipment, but because of civil war, it was not possible to follow up the request. Meanwhile, smallpox vaccination throughout the country all but ceased. In 1965, WHO was again approached with a fully elaborated plan for a 4-year country-wide vaccination campaign, during which smallpox and BCG vaccines would be administered simultaneously. Such a programme had not been attempted before, in part because of the problems inherent in administering BCG vaccine.

Up to 1964, the administration of BCG

Table 18.1. Zaire: number of reported cases of and deaths from smallpox, and case-fatality rates, 1956–1971

Year	Variola major[a]			Variola minor[a]			Total[a]		
	Number of cases	Number of deaths	Case-fatality rate (%)	Number of cases	Number of deaths	Case-fatality rate (%)	Number of cases	Number of deaths	Case-fatality rate (%)
1956	970	157	16.2	3 693	63	1.7	4 663	220	4.7
1957	256	44	17.2	1 694	22	1.3	1 950	66	3.4
1958	57	5	8.8	1 124	11	0.9	1 181	16	1.4
1959	369	44	11.9	2 666	30	1.1	3 035	74	2.4
1960	..	..	..	..	..	..	1 408	..	–
1961	..	..	..	..	..	..	3 624	149	4.1
1962	2 430	498	20.5	1 345	43	3.2	3 775	541	14.3
1963	4 097	668	16.3	1 426	42	2.9	5 523	710	12.8
1964	1 964	136	6.9	1 298	26	2.0	3 262	162	5.0
1965	1 990	255	12.8	1 793	81	4.5	3 783	336	8.9
1966	..	..	..	..	..	..	1 913	171	8.9
1967	..	..	..	..	..	..	1 479	112	7.6
1968	2 995	304	10.1	805	9	1.1	3 800	313	8.2
1969	1 944	207	10.6	128	0	0.0	2 072	207	10.0
1970	–[b]	–[b]	–[b]	–[b]	–[b]	–[b]	716	69	9.6
1971	–[b]	–[b]	–[b]	–[b]	–[b]	–[b]	63[c]	3	4.8

[a] .. = data not recorded.
[b] For reporting purposes, no distinction was made between variola major and variola minor.
[c] Includes 2 cases of chickenpox incorrectly notified as smallpox.

vaccine required that each potential vaccinee should be visited twice, with an interval of 2 days between visits. At the first visit, a non-infectious purified protein derivative (PPD) of the mycobacterium was injected intradermally, and 2 days later the site of injection was examined. The presence of a specified amount of induration at the test site indicated that the child had been infected with tuberculosis. Such children would not benefit from vaccination and thus were excluded from the group given BCG vaccine. The possibility of vaccinating all children, irrespective of whether or not they had had tuberculosis, had been considered, in order to eliminate the cumbersome and time-consuming process of prior testing with PPD. However, the occasional occurrence of unusually severe reactions to vaccine in the already infected group had contraindicated this approach. The WHO Expert Committee on Tuberculosis (1964) discussed the question at length and concluded that, as a practical matter, there was little choice in many countries but to eliminate testing with PPD on the premise that the overall benefits conferred by a logistically simplified BCG vaccination campaign outweighed the risk of a few serious reactions. This change in procedure made it more feasible to administer both vaccines at the same time. Moreover, because UNICEF was supporting many national BCG vaccination campaigns, but not those for smallpox, it was hoped that a combined campaign would elicit from UNICEF material assistance in the form of transport and equipment. The plan called for a national staff of 650, supported by 9 medical advisers, an operations officer, a statistician and an administrator made available by WHO. The magnitude of the programme and the proposed substantial commitment of government resources reflected a degree of interest in smallpox eradication in Zaire that was exceptional in African countries.

The Eradication Programme Begins, 1967–1968

Because of the considerable United Nations and WHO commitment to Zaire, an office in WHO Headquarters rather than in the WHO Regional Office for Africa coordinated the Organization's activities in Zaire until 1968, dealing with such matters as the recruitment of staff and the procurement of supplies. In November 1966, a medical officer from the Smallpox Eradication unit at Headquarters held discussions with national and WHO staff in Zaire and finalized a similar although somewhat more modest plan than that originally proposed by Zaire. Most of the support was to be provided by WHO, UNICEF agreeing to supply only the BCG vaccine, as well as the needles and syringes for its administration.

The overall operational strategy for vaccination was not dissimilar to that in other African countries. It called for 4 large vaccination groups, each composed of 6–8 teams. Each group would be directed by a WHO medical officer and, where available, a Zairian counterpart. Every team would have a supervisor; 3 pairs of vaccinators (a "vaccination unit"), one of each pair giving smallpox vaccine and one BCG vaccine; and a "control unit" of 3 vaccinators and a sanitary agent to visit a sample of the villages one week after vaccination to verify coverage and vaccination results. It was expected that each pair of vaccinators would be able to give 140 smallpox vaccinations and about 70 BCG vaccinations a day. Smallpox vaccination would be performed by scarification and BCG vaccination by intradermal inoculation using a syringe and needle. Village chiefs and local authorities would be notified in advance and asked to bring the people together at a convenient collecting point. In view of tribal and linguistic differences from area to area, local recruitment and the secondment of personnel from existing health services were anticipated.

The WHO senior medical officer was to be designated "co-director" of the programme rather than "adviser", in recognition of the more substantial role that the Organization was intended to play. In addition to the 4 medical officers who were to head the vaccination groups, WHO was also to provide an administrator, a public health nurse and a statistician—in all, 8 staff members, plus short-term consultants. The government complement was expected to amount to 363 persons, of whom 260 would be vaccinators. The cost to the government was set at US$353 800 for the 1967 pilot project and at US$677 000 annually for the principal "attack phase", which was scheduled to extend from 1968 to the end of 1970.

At the outset, WHO provided 34 Land Rovers with trailers, 6 trucks, 5 outboard motors, 14 motor cycles, 10 refrigerators plus

Table 18.2. WHO support for the Zaire programme, 1967–1975 (US$)[a]

Year	Supplies and equipment	Personnel and other costs	Total
1967	160 869	69 428	230 297
1968	48 616	82 238	130 854
1969	259 254	87 674	346 928
1970	99 761	149 097	248 858
1971	28 884	251 046	279 930
1972	120 198	238 488	358 686
1973	78 512	130 402	208 914
1974	78 051	130 043	208 094
1975	37 942	105 065	143 007
Total	912 087	1 243 481	2 155 468

[a] Excluding the cost of 36 878 000 doses of vaccine.

camping gear, office equipment, megaphones and other miscellaneous supplies. WHO's support for this programme up to 1974 represented, on average, about 8.5% of all funds earmarked for smallpox eradication in the Organization's regular budget (Table 18.2).

Following completion of the mass vaccination campaign, it was expected that maintenance vaccination would be continued by the established health units, which by 1972 included 302 hospitals, 45 clinics, 2705 dispensaries and 242 maternity wards. Little attention was paid to reporting and surveillance in the 1966 plan of operations, reflecting the minimal interest in this component of the programme before 1967. As was stated in the plan: "Long-term objectives are to maintain smallpox eradication by appropriate surveillance methods as will emerge from experience and evaluation."

The post of WHO co-director was assigned to Dr Vladimír Zikmund, a WHO epidemiologist already working in Zaire; Dr Lekie Botee, a young Zairian medical officer, was appointed the national co-director – he was to serve in this role with great distinction throughout the early phases of the programme and later, to provide invaluable support as Director-General of Health Services.

The plan called for a pilot programme, to be initiated in 1967, in the course of which 2 groups would administer 2.86 million vaccinations; a full-scale programme, employing 4 operational groups, was scheduled to begin in 1968. Completion of the vaccination phase was foreseen by the end of 1970.

Because of difficulties in organizing so extensive a programme in a country only beginning to recover from civil war, progress was slow at first. Equipment began to arrive in July 1967 and most had been received by October. Two WHO medical officers, already assigned for work in Zaire, were transferred to the programme and a part-time finance officer was made available. At this point, efforts to recruit the remaining promised complement of WHO staff all but ceased. WHO's technical assistance programme in Zaire diminished significantly in scope as from 1967–1968, and responsibility for the Organiza-

Plate 18.1. **A:** Lekie Botee (b. 1930), the first Zairian co-director of the smallpox eradication programme in Zaire; when, later, he became Director-General of Health Services of Zaire he continued to play an active role in the programme. **B:** Pierre Ziegler (b. 1925), WHO co-director from 1968, was instrumental in redirecting operations and in establishing a management system.

tion's activities in Zaire was transferred to the Regional Office for Africa, which had only a small staff, a host of countries to serve and a staggering array of problems. Repeated pleas for additional staff were made but more than a year was to elapse before an administrative officer arrived; not until July 1971 was the promised complement of WHO staff made available.

Preparations for the field programmes were handicapped by the need for the medical officers to spend much of their time on administrative matters, including the creation of a central administrative office, the clearance of supplies through an inefficient customs office and their inventory and storage, and the shipment of vehicles and equipment to provincial capitals which were to serve as bases for field operations. Obtaining the release of government funds was yet another problem which persisted throughout the course of the programme, not infrequently requiring special intervention by the Minister of Health when depleted allocations threatened to stop activities. The part-time WHO finance officer, Mr S. O. Axell, wise in his knowledge of government, eventually obtained agreement to have the allotted funds deposited in a special bank account, and, in time, several such accounts were opened. When delays occurred in obtaining the funds allocated, especially at the beginning of a fiscal year, and the principal account was empty, reserves in the auxiliary accounts were used until the crisis could be resolved.

Because of the difficulties in getting the programme started, the pilot project in 1967 was limited to Kinshasa. It was not an auspicious beginning. The WHO co-director, seeking to ensure a thorough vaccination coverage, proposed that a census should be taken at the same time as the vaccinations were performed so that it could be known precisely what proportion of the population had been vaccinated. Thus, the vaccinators were instructed to prepare a separate card for each family, listing all members by name, age and sex and noting the date of vaccination. Later, an assessor visited each house, issued a special vaccination certificate to each individual successfully vaccinated and revaccinated those whose vaccination had not taken or who had been missed. The process was cumbersome and time-consuming. On average, the vaccinators performed only 20–30 vaccinations a day, and the Kinshasa programme concluded with only 220 000 persons having been vaccinated in a target population of 1 million. Although the methodology was obviously faulty, no changes were made as the programme shifted from the pilot project stage to a mass vaccination campaign.

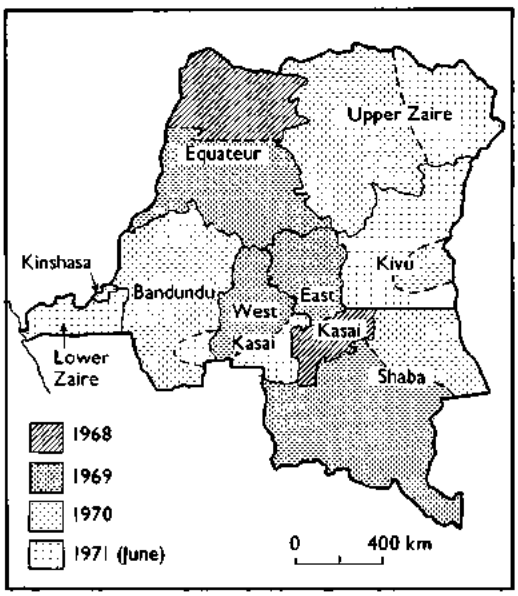

Fig. 18.2. Zaire: areas whose population was vaccinated in the systematic campaign, 1968–1971.

Three vaccination groups had been expected to begin work in 1968, but with only 2 WHO medical officers available to direct them, the programme was launched in only 2 provinces—East Kasai and Equateur (Fig. 18.2). In February, more vaccinators were recruited and trained and, in March, approximately 70 staff began work in East Kasai and 60 in Equateur. On 29 March 1968, a presidential decree gave the programme official status. For smallpox vaccination, most of the staff used the newly available bifurcated needles. In East Kasai, a number of jet injectors, such as were then in use in Brazil and western Africa, were supplied for large-scale vaccination at collecting points.

The jet injectors immediately proved to be widely favoured by the population and permitted the teams to vaccinate many more persons each day. However, the operational problems which characterized the pilot project worsened. The efficiency of the jet injectors was compromised by 3 facets of the programme: (1) the complex enumeration process; (2) the need to distribute vaccination certificates; and (3) the coordination of

smallpox vaccination with the time-consuming intradermal inoculation of BCG using a syringe and needle. Other methods were tried for enumerating the population. Special teams visited each area before vaccination and collected information by house-to-house visits or at collecting points. To simplify the process further, it was decided to record only the names of the heads of households, along with the number of household residents. In addition, efforts were made to persuade village leaders to provide this information. However, it was discovered that the number of people recorded as having been vaccinated in each village was greater than the total enumerated, the discrepancy being accounted for by an inadequate enumeration process and the fact that many individuals from outside the area attended the vaccination sessions. It became apparent that enumeration was a futile exercise. The name of the individual concerned had to be written on each vaccination certificate, after which it was stamped with an official stamp. For each jet injector in operation, on average 6 clerks were required to prepare the certificates. Lastly, the administration of BCG vaccine was an awkward procedure, often requiring, as one observer noted, 2 persons to hold the child and a third to inoculate.

The staffing patterns of the teams were changed to assign more persons to clerical work and to BCG vaccination, but progress remained discouragingly slow. By the end of September, smallpox vaccine had been given to 1 477 000 people and BCG vaccine to 644 000; at this rate the country-wide programme would have taken 8 years to complete.

The Restructuring of the Programme, September 1968

In September 1968, a new WHO co-director—Dr Pierre Ziegler—was appointed. Dr Ziegler had previously served for 16 years in Chad directing a mobile disease prevention and treatment service. During 1967, he worked there with United States Communicable Disease Center staff in the smallpox eradication–measles control programme and understood clearly the practicalities of executing a field programme. Dr Ziegler and Dr Lekie Botee decided to cease the enumeration activities. Instead, a sample survey of 5% of the villages was conducted after 6–8 days to assess the take rates of smallpox vaccination, and again after 2–3 months to assess the take rates of BCG vaccine and overall vaccination coverage. The problem of vaccination certificates proved to be more difficult to deal with because the government insisted on their use and the population was accustomed to receiving them. Procedures for their issuance, however, were greatly facilitated by requiring a member of the team to stamp the certificates and by asking the vaccinee to enter his or her name on the document. Finally, the teams began to use the jet injectors to administer BCG vaccine as well, a recently (albeit incompletely) evaluated technique of BCG vaccination. WHO regional personnel and national tuberculosis advisory staff, in deference to tradition, objected to the adoption of this practice, but eventually acquiesced when Dr Halfdan Mahler, then Chief of the WHO Tuberculosis unit, endorsed it and ordered all to cooperate.

Each vaccination group was reorganized to consist of 5 teams, each with a Land Rover and 5 jet injectors. Every team had 6 members—the team leader, 1 vaccinator for smallpox vaccine and 1 for BCG vaccine, a person to stamp and distribute certificates, another to tally the vaccinees and reconstitute the vaccine, and a driver. One additional team worked with each group to contact the chiefs of all villages 1 or 2 days before the vaccination teams arrived, to explain the programme and to obtain the cooperation of village leaders. An assessment team made up the rest of the field staff.

Each operational group maintained a headquarters in the capital city of the province in which it was working and temporary field camps as it moved through the province. In addition to the field teams, each group had a small administrative unit—a total complement of about 50 persons. Each group was equipped with 10 Land Rovers, 2 trucks, 30 jet injectors and several refrigerators. Each team had specific daily and monthly targets, but was allowed a certain flexibility in its schedule to accommodate the need for frequent long trips by boat and on foot.

The pace of activity began to increase. During the last 3 months of 1968, as many people were vaccinated as during the first 6 months of the programme. By the end of the year, 2 275 000 smallpox vaccinations had been performed over a broad area stretching across the central part of the country. Here, assessment revealed that, except in the most

A Problem Bred by Efficiency

The vaccine standards called for the freeze-dried smallpox vaccine to retain its potency for 30 days when incubated at 37 °C. Thus, in all programmes, provision was made to refrigerate the vaccine at 4 °C at central storage depots and at distribution points in the field to ensure, as far as possible, that vaccine reaching the vaccinee was fully potent. The diluent for the vaccine, however, did not need to be refrigerated. Much of the vaccine provided to WHO came from the USSR, which, like most vaccine manufacturers, packaged both vaccine and diluent in the same box. With this manner of packaging, much more refrigerated storage space was required than if the diluent and vaccine had been packaged separately. Because refrigerated storage facilities were at a premium in all countries, WHO approached the Soviet authorities and proposed that the two should be separately packaged and this was agreed. In 1970, vaccine and diluent began to be distributed in separate boxes, which were clearly marked and had labels of different colours so that there would be no confusion.

Regrettably, the change in the manner of packaging was not at first noted in Zaire until a vaccination team, after 3 weeks' journey into the forest, opened the boxes to begin a vaccination campaign—only to find that they had brought with them nothing but diluent.

isolated districts, more than 90% of the population were being vaccinated. On average, each team was able to administer daily 1200 smallpox vaccinations and 600 BCG vaccinations. In only a few months, Dr Ziegler and Dr Lekie Botee, assisted by 2 WHO group leaders, Dr P. Cartagena and Dr E. Zanotto, had transformed a chaotic operation into a remarkably efficient machine.

In January 1969, the programme began to publish a monthly surveillance bulletin, which was distributed to 943 health units throughout the country. It documented the numbers of cases reported from each province and the progress of the campaign, exhorted all to report cases of smallpox, and urged health units to undertake vaccination.

Until 1969, few of the personnel in the extensive network of health centres, clinics and hospitals had administered vaccines of any type. Those who had done so had been supplied with either liquid smallpox vaccine or a substandard freeze-dried product produced by a laboratory in Lubumbashi. A WHO consultant was recruited to determine whether, with assistance, the laboratory could produce satisfactory vaccine, but the problems were too numerous and the laboratory was closed. In June 1969, it was agreed that only vaccine that met WHO requirements would be used, and thereafter vaccine supplied by WHO, emanating principally from the USSR, replaced the local product. With the continuing encouragement of the smallpox eradication programme staff, the numbers of smallpox vaccinations performed in health centres and clinics increased from 575 000 in 1968 to 3 575 000 in 1969, although some health centre staff, preoccupied with curative medicine, refused to participate in the campaign.

In February 1969, Mr A. Samy, an administrator, was recruited by WHO. A resourceful and experienced person, he soon established a sophisticated vehicle repair and maintenance workshop—a necessity because, as noted in a report: "Despite more than 3000 Land Rovers in service in the country, the after-sales service provided is inadequate as for repair and often nonexistent concerning locally available spare parts." Records of repair and maintenance schedules were established for all vehicles, mechanics were recruited and trained, and trailers were rebuilt to permit them to carry petrol, often unavailable in remote parts of Zaire. A workshop for repair of the jet injectors was also established, along with an inventory of spare parts.

The logistic and operational problems were formidable but programme staff, with ingenuity and persistence, competently dealt with them. The recruitment of the required WHO staff, the placement of orders for equipment and the arrangements for its shipment were, however, beyond their control, these tasks being the responsibility of the WHO regional office. All were greatly delayed. Even the use of BCG vaccine had to be

Plate 18.2. **A:** The protracted fighting in Zaire devastated the road system, and vehicles frequently became mired along bush trails. **B:** Broken chassis were common; without a special repair and maintenance workshop, the programme would have foundered.

interrupted for a period when UNICEF decided to send the vaccine by air but the diluent for reconstituting it by sea. The only supplies which did not present a problem were smallpox vaccine, bifurcated needles and jet injectors. These could be provided promptly, on request, from a reserve stockpile held at WHO Headquarters.

In January 1969, Dr Ziegler and Dr Lekie Botee decided—and the government supported them with an appropriate request to the regional office—that persons with qualifications similar to those of staff employed by the United States Communicable Disease Center in western Africa should be recruited as WHO operations officers. It was expected that they would organize provincial surveillance teams so as to strengthen reporting and investigate outbreaks. WHO agreed to recruit 5 such persons, but more than 2 years were to elapse before 4 of the 5 arrived. Meanwhile, with only 2 WHO medical officers available for field work and no Zairian staff who could independently supervise field activities, Dr Ziegler and Dr Lekie Botee had no option but to pursue the vaccination campaign, postponing surveillance until adequate staff became available.

The vaccination campaign steadily gained momentum: between April and June 1969 an average of about 500 000 smallpox vaccinations were administered each month, compared with only 200 000 a month the year before. In July, a third vaccination group was able to begin work under the supervision of a WHO medical officer recruited from among the foreign medical staff remaining in Zaire. He was replaced later that year by the first of the WHO operations officers, Mr Garry Presthus, who was to provide able assistance first in Zaire and later in Botswana. By the end of 1969, more than 8 million persons had received smallpox vaccine and almost 3.5 million BCG vaccine (Fig. 18.3). The total was less than the optimistic target projected in 1966, but the gap was narrowing. The results of continuing assessment showed a vacci-

Table 18.3. Zaire: number of reported cases of smallpox, by province and year, 1967–1971

Province	Number of cases				
	1967	1968	1969	1970	1971
Bandundu	145	983	401	126	0
East Kasai	327	618	23	17	1
Equateur	61	10	70	8	0
Kinshasa	0	124	31	4	0
Kivu	235	339	293	401	35
Lower Zaire	26	33	50	13	15
Shaba	391	1 391	898	64	7
Upper Zaire	25	44	236	83	3
West Kasai	269	258	70	0	2[a]
Total	1 479	3 800	2 072	716	63[a]

[a] Two cases of chickenpox incorrectly notified as smallpox.

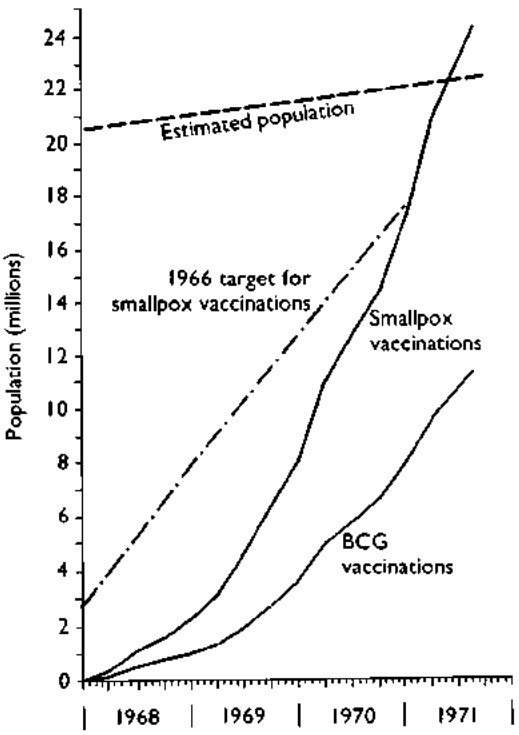

Fig. 18.3. Zaire: estimated population and numbers of smallpox and BCG vaccinations performed from 1968 to June 1971, compared with the 1966 target for smallpox vaccinations.

nation coverage which frequently exceeded 95% and was never below 80%.

The number of recorded cases decreased from 3800 in 1968 to 2072 in 1969 (Table 18.3; Fig. 18.4), a significant reduction in view of the fact that more medical units, encouraged through the monthly surveillance bulletin, began to report each week the number of cases of smallpox seen. During 1969, an average of 87 medical units out of an estimated 535 provided weekly reports—a far from optimum response but an improvement over 1968. The highest proportion of reports was received from the provinces in which the vaccination groups had worked and the medical units had been most thoroughly briefed about the programme. In East Kasai Province, in which the vaccination campaign was completed in February 1969, the results were dramatic (Fig. 18.5).

The Vaccination Campaign Becomes Fully Established, 1970

Most of the supplies and equipment had been received by 1969 (Table 18.4), sufficient to meet the needs of 4 vaccination groups, but it was not possible to establish a fourth group

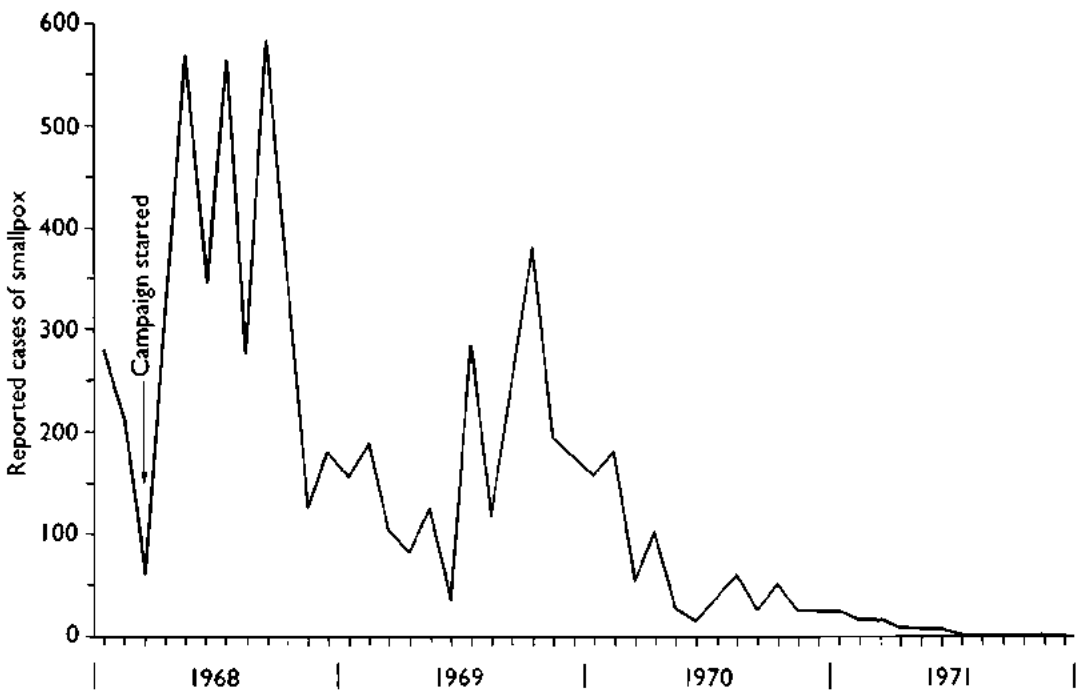

Fig. 18.4. Zaire: number of reported cases of smallpox, by month, 1968–1971.

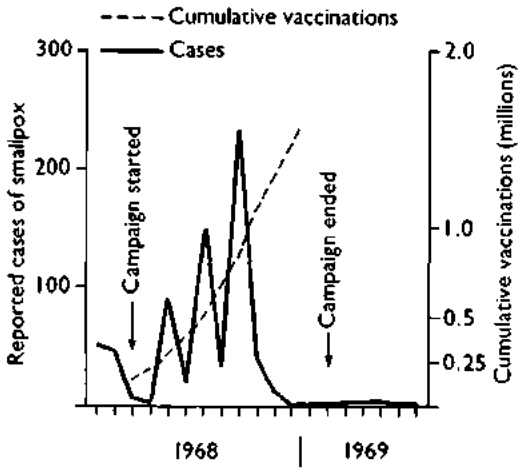

Fig. 18.5. East Kasai Province: number of reported cases of smallpox and number of vaccinations performed, by month, 1968–1969.

Table 18.5. Zaire: smallpox eradication programme staff, by category and year, 1968–1972

Category	Numbers at end of year				
	1968	1969	1970	1971	1972
National staff:					
Medical officers	1	1	1	1	1
Office clerks/typists	13	12	14	10	11
Supervisors	0	2	4	0	0
Team leaders	13	13	25	9	11
Vaccinators	51	55	92	10	11
Drivers/mechanics	25	34	60	18	21
Others	23	24	38	26	28
Total	126	141	234	74	83
WHO staff:					
Medical officers	3	4	5	5	3
Administrative officers	1	2	2	2	1
Operations officers	0	1	2	5	3
Total	4	7	9	12	7
United States Peace Corps volunteers	0	0	0	8	8
Total	130	148	243	94	98

until February 1970, when Dr Ziegler succeeded in arranging for the transfer of another locally employed foreign medical officer, Dr A. Hornbanger. In just 8 weeks Dr Hornbanger's group of 7 teams, based in Kinshasa, performed more than 1.6 million smallpox vaccinations and 800 000 BCG vaccinations in the city; during March, each team of 6 persons gave, on average, 5300 smallpox vaccinations and 2800 BCG vaccinations a day.

With 4 groups in the field, the complement of national personnel increased until it reached its highest number—234 persons—a ratio of 1 staff member for about 100 000 inhabitants (Table 18.5). There were 9 international staff. The vaccination campaign progressed rapidly despite the fact that groups were beginning to spend more time in the least accessible regions of the country, where travel by boat and on foot was frequently required. For example, one group, consisting of 50 persons, which had succeeded in vaccinating 915 000 people in one month in an accessible, more populated, area, was able to vaccinate only 54 000 people during the succeeding month.

By the end of 1970, 17 million persons had been vaccinated against smallpox and systematic programmes had been completed throughout the country except in areas in which security had been a problem, and in Lower Zaire, near Kinshasa, in which few cases were being detected and which, accordingly, had lower priority.

Table 18.4. Zaire: inventory of major equipment, by year, 1968–1972

	1968	1969	1970	1971	1972
Vehicles	48	52	65	65	73
Motor cycles	92	92	92	0	0
Motorboats	5	6	10	10	12
Freezers	0	3	17	17	13
Refrigerators	12	15	15	12	9
Jet injectors	37	143	143	143	143

The Problem of Surveillance

Dr Ziegler and Dr Lekie Botee continued to worry about reporting and surveillance. The recruitment of operations officers who could lead surveillance–containment teams had been expected but the arrival of only one such officer, late in 1969, was of little help. The creation of a national team was considered but, in a country so large and with travel so difficult, it was decided that this would be unproductive. Moreover, communications were a major problem, so that even when cases were discovered notification was so greatly delayed that it was difficult for a single team to be effective. For example, a telegraphic message sent in April, reporting cases in a province adjacent to Kinshasa, took a month to reach Kinshasa.

Each of the health units throughout the country continued to be encouraged to vaccinate, to report cases and to contain outbreaks. Although the average number of reports received each week increased from 87 in 1969

Table 18.6. Zaire: number of reported cases of smallpox, by province and month, 1970 and 1971

Province	1970												1971									
	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sept.	Oct.
Bandundu	53	54	1	0	4	0	2	6	0	0	6	0	0	0	0	0	0	0	0	0	0	0
East Kasai	0	1	1	2	0	5	0	0	2	6	0	0	0	0	1	0	0	0	0	0	0	0
Equateur	0	1	2	0	0	0	3	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0
Kinshasa	1	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Kivu	93	78	21	61	1	10	19	51	5	32	13	17	9	9	10	3	4	0	0	0	0	0
Lower Zaire	0	3	0	0	0	0	0	0	0	1	5	4	15	0	0	0	0	0	0	0	0	0
Shaba	5	18	12	5	0	1	3	3	8	6	0	3	1	2	0	3	1	0	0	0	0	0
Upper Zaire	1	12	12	27	20	1	1	4	2	1	2	0	0	1	1	0	0	1	0	0	0	0
West Kasai	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2[a]	0	0
Total	153	167	50	97	25	17	28	64	17	48	26	24	25	12	12	6	5	1	0	2[a]	0	0

[a] Two cases of chickenpox incorrectly notified as smallpox.

to 140 in 1970, there were still many units which did not report at all.

During 1970, only 716 cases were reported, the lowest total recorded in Zaire since a national reporting system had been introduced. By September, fewer than 50 cases a month were being discovered, most of them in eastern Kivu Province (Table 18.6), in which the vaccination campaign was still in progress. At least some of the reported cases were thought to be chickenpox, since they were noted as having occurred in young children with a distinctive vaccination scar. In the hope of getting a more accurate assessment of this problem, Dr Ziegler and Dr Lekie Botee decided to distribute collection kits and to ask those who reported cases to submit specimens for examination by WHO reference laboratories. However, the distribution of the kits, as well as their return, proved troublesome because of the poor postal service.

Frustrated by WHO's inaction in recruiting staff, Dr Lekie Botee and Dr Ziegler in Kinshasa and Henderson, on a special trip to Washington, approached the United States government, requesting the assignment of 8 Peace Corps volunteers from the USA. This had to be done unofficially, because at that time it was the policy of WHO that the assignment of national volunteers should be decided on and worked out by agreement between the national governments concerned. WHO staff were to play no role in encouraging their assignment in any country or in supporting their activities. However, the Zaire programme was desperate for personnel to undertake surveillance activities and there appeared to be no other alternative. United States officials were themselves not initially enthusiastic about the proposal because of their policy of assigning Peace Corps volunteers to specific areas in which they would become acquainted with the local people during their tour of duty. The surveillance teams, in contrast, were expected to travel constantly over an extensive area. Moreover, the task of supervising a surveillance team was felt to be unusually demanding. Reluctantly, the USA agreed to select Peace Corps volunteers who had performed especially well during a 2-year assignment and wished to extend their tour of duty for a year or more. Those appointed were to prove invaluable.

The Discovery of a Case of Monkeypox in a Human Being

The imperative need for surveillance was heightened by the identification in October 1970 of the first recognized case of monkeypox in a human being. The WHO reference laboratory in Moscow isolated monkeypox virus from a specimen collected from a child who had become ill on 22 August 1970. The virus had been isolated previously from outbreaks of disease in captive monkeys but never before from a human (see Chapter 29). Nothing was known about the possible clinical manifestations in humans or about the potentialities for spread from human to human. Recalling that yellow fever eradication had been thwarted in the 1930s when a natural reservoir in mammals had been discovered, WHO staff were deeply concerned that monkeypox virus might be analogous to sylvan yellow fever virus, perhaps dooming the objective of global eradication. Concern grew when, within a week, 4 cases in Liberia were confirmed as monkeypox by the WHO reference laboratory in Atlanta, USA.

Ladnyi, at that time the WHO intercountry smallpox adviser in eastern and

Plate 18.3. Kalisa Ruti (b. 1948) examining a patient with monkeypox. He succeeded Lekie Botee as co-director of the smallpox eradication programme in Zaire and subsequently supervised the extensive investigation of monkeypox.

southern Africa, joined Dr Ziegler early in January 1971 to investigate the case in Zaire. The child, a 9-month-old boy, had been admitted on 1 September to a hospital in Basankusu, a small town in the central part of Equateur Province. He had a rash with a distribution like that of smallpox but because the lesions were haemorrhagic, the physician was uncertain of the diagnosis and had taken a specimen. After admission the child developed enlarged cervical glands as well as otitis and mastoiditis. Subsequently, he contracted measles and died on 29 October. Ladnyi and Dr Ziegler searched for other cases with rash in Basankusu town and in the village in which the child had lived until 4 days before becoming ill. No cases could be found, although it was ascertained that the family of the patient occasionally ate monkeys, as did many other people in the area.

The nature of the area and the difficulties of travel and communication in this and many other parts of Zaire is conveyed in the report of Ladnyi and Dr Ziegler. Equateur Province was made up of 4 districts, each district consisting of a number of territories, of which Basankusu Territory was one. To travel from Kinshasa to Mbandaka, the provincial capital, and from there to Basankusu town was difficult. A weekly air flight, often cancelled, connected Kinshasa with the two towns. Travel by road meant crossing no fewer than 20 lakes and rivers, only some of which had a regular ferry service. Twice monthly, a river-boat made a 2-day trip to Mbandaka, where, after a wait of several days, one could transfer to another boat for a further 2-day trip to Basankusu. A cable to Kinshasa often took a month or longer to deliver. Basankusu Territory covered an area of 20 000 square kilometres and had a population of 62 000, mainly primitive farmers living in small villages scattered along paths and tracks in dense tropical rain forest. The distance from the capital of the territory to the most remote villages was 150 kilometres. Only one all-weather road crossed the territory, intersected by several impassable rivers with neither bridges nor regular ferry services. Travel along the tracks and paths was difficult, the so-called rainy season being 10 months long; even in the drier months, rain fell 2 or 3 days a week.

Basankusu Territory was served by a government hospital and 18 dispensaries scattered throughout the area, some operated by government health staff and some by missionaries. Smallpox had been present in the district in 1968 but no cases were known to have occurred in 1969. Two cases had been reported in 1970, one of which was discovered to have been chickenpox; the other was the case of monkeypox.

Vaccination had been performed by the teams in 1969, but no special containment vaccination programme had been conducted after discovery of the monkeypox case. Ladnyi and Dr Ziegler carried out a vaccination scar survey in 6 villages near where the patient lived, 115 kilometres from Basankusu town. The results are indicative of the thoroughness of the vaccination campaign (Table 18.7).

Twenty-one persons had characteristic residual pockmarks of smallpox but their illnesses had all occurred before or during 1968,

Table 18.7. Basankusu Territory: results of vaccination scar survey, by age group, 1970

Age group (years)	Number assessed	Subjects with vaccination scars	
		Number	%
0–4	186	159	85.5
5–15	358	339	94.7
≥ 16	588	567	96.4
Total	1 132	1 065	94.1

when smallpox had been widely prevalent. In this instance, at least, monkeypox appeared not to have spread to other human beings. The results of this and subsequent investigations of cases of monkeypox are described in Chapter 29. Eventually the studies confirmed that cases of monkeypox in humans were rare and that the disease spread only with difficulty from human to human.

The Creation of a Surveillance Programme, 1971

In January 1971, 5 provincial surveillance teams were established with the eventual arrival of 2 additional WHO operations officers and 3 United States Peace Corps volunteers. One of the 2 operations officers, Mr Mark Szczeniowski, was to remain with the programme in Zaire over the following 15 years, continuing the programme of surveillance and supervising special investigations of monkeypox. Each of the teams had a vehicle, a driver, a Zairian counterpart and a vaccinator. Each was equipped with a 100-watt transceiver in order to communicate rapidly with Kinshasa, with their provincial base of operations, and with each other. In their respective areas, they began to visit in a systematic fashion all hospitals, dispensaries and health centres to inquire about possible cases, to request immediate notification of any suspected case, to distribute vaccine and needles and to encourage each establishment to vaccinate everyone who attended it. Each health facility was visited once or twice every 6 months. The teams investigated all suspected cases and obtained specimens. In addition, in different villages they undertook a random scar survey assessment of about 2000 persons each month to assess the status of vaccinial immunity. Each team spent 21 days in constant travel, followed by a week's holiday.

By July 1971, 11 surveillance teams were in operation; 2 were assigned to each of the 3 largest provinces, and 1 each to the smaller ones. With the termination of the vaccination campaign at the end of July, the numbers of national staff were reduced and the medical officers who had served as group leaders each assumed supervisory responsibility for several provinces.

During the vaccination campaign, more than 24.3 million persons were vaccinated against smallpox and 11.4 million received

Plate 18.4. The surveillance programme in Zaire began in January 1971 and continued into the 1980s as teams sought human cases of monkeypox, a disease clinically almost identical to smallpox. Schoolchildren were shown pictures of smallpox in the WHO pictorial guides and asked if they had seen any cases.

Table 18.8. Zaire: population and number of reported smallpox and BCG vaccinations, by province, March 1968–July 1971

Province	Population, 1971 estimate[a] (thousands)	Number of vaccinations performed		Period
		Smallpox	BCG	
Bandundu	2 672	2 630 261	1 364 991	June 1970–Jan. 1971
East Kasai	1 922	1 659 454	589 277	March 1968–Feb. 1969
Equateur	2 497	2 593 747	1 006 667	March 1968–Dec. 1969
Kinshasa	1 359	1 802 151	951 430	Feb. 1970–May 1970
Kivu	3 452	4 675 079	2 258 582	Sept. 1970–July 1971
Lower Zaire	1 544	1 756 221	949 430	Jan. 1971–June 1971
Shaba	2 828	3 869 180	2 003 529	April 1969–June 1970
Upper Zaire	3 446	3 524 230	1 405 349	Feb. 1970–May 1971
West Kasai	2 499	1 836 095	827 673	July 1969–May 1970
Total	22 219	24 346 418	11 356 928	

[a] Derived from United Nations (1985).

BCG vaccine (Table 18.8). All parts of the country had been reached except for a small area in Kivu Province with a population of 115 000 persons. Even there, where security remained a problem, the staff were able to vaccinate some 50 000 people, although not in the systematic manner in which the rest of the campaign had been conducted.

The number of cases diminished rapidly during 1971. No cases were discovered in July and only 2 in August—the last reported cases in Zaire. The occurrence of these 2 cases, in West Kasai Province, long after any previous notifications there, was most puzzling. Extensive investigation, however, revealed that they were cases of chickenpox. Thus, a case in June in Upper Zaire appears to have been the last in the country, occurring just as the vaccination campaign concluded.

By the time this last case had occurred, Zaire's only infected neighbour was the Sudan, in which cases continued to occur in border areas until December 1972. No importations were detected in Zaire, despite continuing, intensive search by a specially assigned surveillance team headed by one of the WHO medical officers.

Data regarding the age and vaccination status are available for 2124 cases that occurred between 1969 and 1971 (Table 18.9).

The surveillance teams, with a staff of 95, continued to function until eradication was certified in Zaire in 1977, although international staff were gradually replaced by experienced Zairian counterparts. A special programme for the surveillance and investigation of monkeypox continued through 1986 (see Chapter 29).

Between 1971 and July 1976, nearly 700 specimens were collected, of which 3 (in 1971) contained variola virus, 9 contained monkeypox virus, 88 contained viruses of the herpes–varicella group and 6 contained either vaccinia virus or tanapox virus (Table 18.10).

Table 18.9. Zaire: number of reported cases of smallpox, by age group and vaccination status, 1969–1971[a]

Age group (years)	Cases		With vaccination scar	
	Number	% of total	Number	% of cases
<1	360	16.9	—	—
1–4	758	35.7	78	10.3
5–14	548	25.8	84	15.3
⩾15	458	21.6	155	33.8
Total	2 124	100.0	317	14.9

[a] Details are not available for 725 other cases of smallpox reported during this period; in addition, 2 incorrectly notified cases of chickenpox have been omitted from consideration.

Eventually, the teams were successful in obtaining the cooperation of all but a few of the 3289 health establishments in performing vaccinations. A surprisingly large number of vaccinations were given (Table 18.11), especially after the surveillance teams began their regular schedule of visits in 1971.

As Dr Ziegler was to observe, many staff working in rural dispensaries had not been

Plate 18.5. A: The roads in Zaire varied widely in character, some consisting only of logs laid along forest paths. **B:** Communication between smallpox eradication headquarters in Kinshasa and the surveillance teams relied on 100-watt transceivers built into trailers. Garry Presthus, shown here, was the first WHO operations officer to be recruited. Later he served as a smallpox adviser in Botswana. ▷

Z. JEŽEK

BY COURTESY OF G. PRESTHUS

WHO / J. G. BREMAN

Plate 18.6. Nomadic groups, who ranged widely over large areas of central and northern Sudan, sometimes carried smallpox over long distances. Here, a surveillance worker with a WHO smallpox recognition card questions a group about possible cases.

Table 18.10. Zaire: results of laboratory examination of specimens, 1971–1976[a]

Year	Number of specimens examined	Laboratory diagnosis			
		Variola virus	Monkeypox virus	Herpes-varicella viruses	Vaccinia and tanapox viruses
1971	168	3	0	0	0
1972	138	0	3	11	2
1973	89	0	2	18	1
1974	53	0	1	15	1
1975	189	0	2	25	1
1976 (July)	54	0	1	19	1

[a] Recorded according to the year of collection of the specimens; in Table 24.1 (Chapter 24), the specimens tested have been recorded according to the year of their receipt by WHO in Geneva.

Table 18.11. Zaire: number of smallpox vaccinations performed by health establishments, 1968–1975

Year	Number of vaccinations
1968	575 573
1969	3 574 245
1970	2 681 330
1971	2 869 222
1972	4 080 313
1973	4 960 815
1974	3 089 989
1975	2 562 752

Table 18.12. Zaire: results of vaccination scar surveys, by age group and province, 1972 and 1974

Province	Percentage with vaccination scars (total number examined = 505 802)		
	<1 year	1–14 years	⩾15 years
1972			
Bandundu	22	87	90
East Kasai	20	78	77
Equateur	26	89	96
Kinshasa	65	95	97
Kivu	20	86	88
Lower Zaire	25	96	96
Shaba	48	85	84
Upper Zaire	47	95	99
West Kasai	25	86	81

Province	Percentage with vaccination scars (total number examined = 61 633)			
	<1 year	1–4 years	5–14 years	⩾15 years
1974				
Bandundu	56	84	96	98
East Kasai	34	85	96	99
Equateur	45	75	89	96
Kinshasa	81	100	94	94
Kivu	64	89	95	98
Lower Zaire	74	91	94	98
Shaba	66	88	96	95
Upper Zaire	66	90	98	99
West Kasai	32	85	93	96

Table 18.13. Zaire: receipt of weekly epidemiological reports, 1975–1976

Year	Quarter	Number of weeks	Number of reports expected	Reports received	
				Number	%
1975	1st	11	238	194	81.5
	2nd	12	238	183	76.9
	3rd	13	238	185	77.7
	4th	14	238	184	77.3
1976	1st	11	238	180	75.6
	2nd	12	238	193	81.1
	3rd	13	238	169	71.0
	4th	14	238	196	82.4

visited by a physician or nurse for 10 years or more. They responded enthusiastically to the visits of the surveillance teams and many conscientiously undertook to sustain high levels of vaccinial immunity, not only among the people coming to their dispensaries but among the inhabitants of nearby villages as well. The results as measured by scar surveys in 1972 and again in 1974 confirm the success of this effort (Table 18.12).

Eventually 238 reporting sites were identified and charged with the responsibility of reporting weekly any suspected cases of smallpox and chickenpox. This network, which included 92 hospitals, 39 health centres, 54 dispensaries and 48 district or provincial health and medical units, ultimately served as a national morbidity reporting system. The response was remarkably good considering the difficulties of communication (Table 18.13).

During the surveillance period, the mobile teams with their transceivers provided a mechanism for the emergency reporting of outbreaks of other diseases, such as plague, yellow fever and cerebrospinal meningitis. Often the teams themselves participated in special programmes to control these outbreaks.

SUDAN

Background

The Sudan, even larger in area than Zaire, was no less important geographically to the strategy of the eradication programme—but for different reasons. Following a mass vaccination campaign conducted during 1961–1963, the Sudan became free of smallpox and is believed to have remained non-endemic until 1968. However, the risk of the disease being imported into the country and becoming re-established was high. Traditional caravan routes between Mecca and the endemic countries of western Africa crossed the north-central area of the Sudan and, historically, many outbreaks had been traced to cases imported by such travellers. To the east lay heavily endemic Ethiopia, whence came some 200 000 seasonal labourers each year for the harvesting of *dura* (sorghum). In addition, because of civil war in northern Ethiopia, thousands of refugees from Eritrea had moved across the Sudan's north-eastern borders, many of them returning periodically to Ethiopia. In the southern part of the Sudan, a civil war had been in progress since 1956 and many refugees frequently travelled between the Sudan and camps in Uganda and Zaire.

In 1967, the Sudan expressed interest in participating in the smallpox eradication programme, the principal component of which would be a campaign during which, as in Zaire, BCG vaccine would be administered at the same time as smallpox vaccine. The programme, however, did not begin until 1969 and proceeded slowly thereafter, the logistics of administering the two vaccines at the same time never being satisfactorily worked out.

Meanwhile, 9 cases of smallpox thought to be importations occurred in 1967, and during the first few months of 1968, 104 cases were detected. Investigation suggested that they were attributable to an importation from Ethiopia. No cases were discovered after June and it was thought that the outbreak had been satisfactorily contained. However, cases were again detected in December 1968 and in the early months of 1969 in many of the same areas. Once more, special investigations were undertaken. In all, 119 cases were documented but it was believed that there were many others which had not been detected. Although the initial outbreaks had occurred near the Ethiopian border, it was clear that many had originated in rural areas of the southern Sudan, unreachable because of civil war. It was suspected that endemic smallpox had become re-established and, in 1970, this became a certainty as the disease spread widely across the country.

Repeated attempts had been made to persuade WHO advisers and senior Sudanese staff that a continuing programme of surveillance and containment was vitally important in a country which was thought to be smallpox-free, but little was done until 1972. A seminar held in December 1971 marked a turning-point. A Sudanese medical officer, Dr Omer Sulieman, rapidly organized a surveillance–containment programme in the north, beginning in January 1972. In April, he moved to the south on conclusion of the civil war. Working with extraordinary energy and skill, he and Sudanese programme staff stopped transmission in December 1972. Subsequently, programme staff conducted a thorough search and vaccination campaign over extensive areas along the Ethiopian border in collaboration with Ethiopian staff, and at times assisted the programme in Ethiopia through search and case investigation far inside the frontiers of that country.

There was some speculation that the Sudan had never been smallpox-free, that transmission had always continued in inaccessible areas of the war-torn southern provinces. In retrospect, however, the epidemiological data strongly support the belief that transmission in the Sudan was interrupted in 1962 and endemic smallpox did not recur until after the importations of 1967–1968.

Population Movements

The Sudan is diverse in character, with extensive desert throughout the north giving way to steppe and grassland in the central part of the country and to large marshes and tropical forest areas in the south-eastern and southern parts of the country. The White Nile extends the length of the country, some 2000 kilometres, providing river transport and irrigation in the east central region. It is joined at Khartoum, the capital, by the Blue Nile, which flows from Ethiopia. Nearly half of the Sudan's 12.9 million population (in 1967) live in the fertile, extensively irrigated areas of Khartoum, Kordofan and Blue Nile Provinces near the confluence of the two rivers (Fig. 18.6).

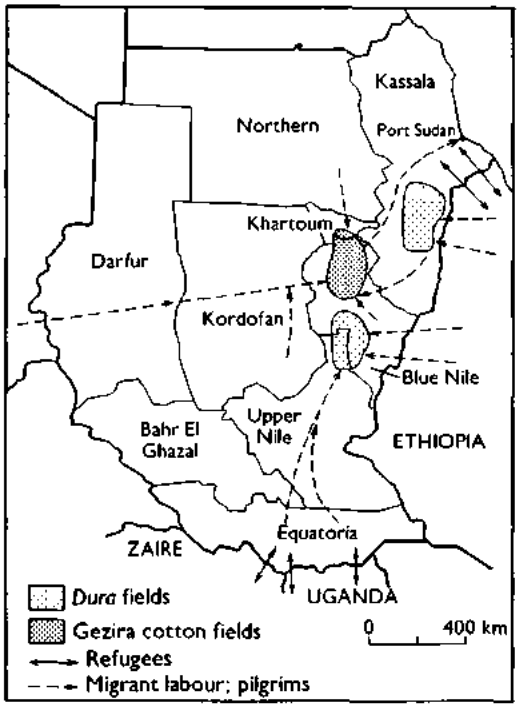

Fig. 18.6 Sudan: movement of refugees and seasonal populations.

The seasonal migration of agricultural workers was a significant factor in the spread of smallpox within the country and in the importation of the disease from Ethiopia. South of Khartoum were the great cotton fields of the Gezira Irrigation Scheme, which employed some 350 000 workers between mid-December and May. The labour force consisted largely of Sudanese workers recruited in various provinces and transported in large groups to and from the area by truck and boat. As important were the *dura* fields in Kassala, Blue Nile and Upper Nile Provinces, which attracted some 400 000 seasonal labourers, most of whom were employed for the harvest during December–February. Half of the workers came from Ethiopia, many of them travelling on foot for as long as 2–3 weeks to reach the area.

Other factors contributed to the movement of population and the spread of smallpox. Some 1.5 million pastoral nomads roamed the central and northern regions of the Sudan. In the north-east, upwards of 100 000 Ethiopian refugees from Eritrea camped near border areas but moved in and out of the country. Additionally, each year 30 000–40 000 pilgrims to Mecca from western Africa travelled across the country, through Khartoum. Population movements, overall, were far more extensive than in other Saharan and sub-Saharan African countries.

Civil war in the 3 southernmost provinces, which began at the time of independence in 1956, when tribal populations revolted against traditional leadership, was another serious problem. An estimated 50 000–100 000 Sudanese refugees from Equatoria Province lived in northern Uganda and Zaire but regularly moved in and out of the Sudan. Until March 1972, when a peace treaty was signed, much of the rural area in these southern provinces could be penetrated only by military convoy; health activities, including smallpox vaccination, were few; roads and bridges were destroyed or deteriorated.

Health facilities were reasonably numerous in the Sudan, although in a country so large they were widely dispersed. A tabulation drawn up in 1976 listed 127 hospitals, 159 health centres, 590 dispensaries and 1214 dressing stations.

Smallpox in the Sudan before 1968

Records of cases of and deaths from smallpox have been available since 1925. Up to the end of 1958, these show case-fatality rates in most years of 10–20%, with between 12 and almost 6500 cases reported each year. Major outbreaks occurred sporadically, the last being recorded during the period 1952–1955 in Darfur Province and the 3 southern provinces. Mass vaccination campaigns were conducted whenever outbreaks developed. Each year, 500 000–2 000 000 persons were vaccinated with liquid vaccine produced at a laboratory in Khartoum. Routine vaccination was rarely performed by the health units but enough persons were being vaccinated in mass campaigns to discourage the practice of variolation, which had once been widely prevalent.

In 1959 case-fatality rates abruptly declined (Table 18.14), falling to levels typical of those of variola minor. Since most of the cases during that year and the 3 subsequent years were recorded in Blue Nile Province, adjacent to Ethiopia, it is probable that the virus strain originated in that country.

Following the decision of the Twelfth World Health Assembly, in May 1959, to carry out global smallpox eradication, the Sudanese government requested assistance

Table 18.14. Sudan: number of reported cases of and deaths from smallpox, and case-fatality rates, 1952–1972

Year	Number of cases	Number of deaths	Case-fatality rate (%)
1952	3 670	578	15.7
1953	3 030	221	7.3
1954	4 200	584	13.9
1955	1 427	284	19.9
1956	25	4	16.0
1957	295	23	7.8
1958	380	90	23.7
1959	336	9	2.7
1960	162	0	0
1961	8	0	0
1962	95	0	0
1963	0	0	0
1964	0	0	0
1965	69	9	13.0
1966	0	0	0
1967	9	0	0
1968	106	0	0
1969	130	0	0
1970	1 051	15	1.4
1971	1 141	10	0.9
1972	827	10	1.2

from WHO to undertake a national vaccination campaign. WHO provided US$12 000 for vehicles and refrigerators and the USSR contributed freeze-dried vaccine. Except for this support, the programme was entirely a national effort, utilizing temporary staff who vaccinated by house-to-house visits and, in some areas, at collecting points. The transport provided by WHO was supplemented by rented vehicles and some provided by the military. During a 3-year period (1962–1964) 8 840 152 vaccinations were performed, a number equivalent to about 75% of the total population. The central and northern provinces were much better vaccinated than the 3 war-ridden southern provinces: in Upper Nile and Bar el Ghazal Provinces the coverage was very limited and in Equatoria Province it was nonexistent.

Although many persons remained unvaccinated, the campaign was successful in controlling smallpox. Except for an outbreak of 69 cases in Darfur Province in 1965 and 9 cases in 1967, no cases were reported in the Sudan during the years 1963–1967. Following the mass campaign, the numbers of vaccinations again fell off, averaging just 500 000 per year from 1964 to 1967, and because liquid vaccine was again employed, it is probable that only a small proportion were successful.

The Decision to Undertake an Eradication Programme, 1967

Because so few people were vaccinated after 1964, it was assumed in 1967 that few of those under the age of 5 years had ever been successfully vaccinated and that large numbers throughout rural areas of the southern provinces remained susceptible. No cases were being detected by staff of the comparatively extensive infrastructure of health services but concern was expressed that smallpox, if imported, might recur in epidemic form. Accordingly, it was decided in June 1967 to undertake another 3-year national vaccination campaign, and Dr Abdel Hamid El Sayed Osman was placed in charge. The inhabitants of provinces in the central region (Table 18.15) would be vaccinated first, followed in the second year by those of the

Table 18.15. Sudan: population and number of reported cases of smallpox, by region and province and by year, 1966–1973

Region and province	Population, 1970[a] (thousands)	Number of cases							
		1966	1967	1968	1969	1970	1971	1972	1973
Northern region:									
Northern	912	0	0	0	0	2	1	0	0
Kassala	1 450	0	0	9	0	89	281	111	0
Khartoum	1 066	0	7	2	7	261	22	7	0
Central region:									
Blue Nile	3 481	0	0	19	35	195	252	13	0
Kordofan	2 010	0	0	0	0	67	17	55	0
Darfur	1 991	0	0	0	0	0	17	5	0
Southern region:									
Upper Nile	690	0	2	76	76	106	78	1	0
Bahr El Ghazal	1 275	0	0	0	0	177	316	216	0
Equatoria	729	0	0	0	12	154	157	419	0
Total	13 604	0	9	106	130	1 051	1 141	827	0

[a] Estimates based on official government data, 1973.

Table 18.16. WHO support and national contribution to the Sudan programme, 1967–1976 (US$)[a]

Year	WHO support			Government contribution
	Personnel	Supplies, equipment and local costs[b]	Total	
1967	18 709	104 213	122 922	272 832
1968	18 638	52 323	70 961	459 506
1969	40 810	19 446	60 256	746 697
1970	47 261	5 523	52 784	1 148 765
1971	44 669	34 140	78 809	1 005 169
1972	31 089	24 453	55 542	1 076 967
1973	18 664	34 108	52 772	1 134 406
1974	19 913	56 750	76 663	1 005 169
1975	46 002	84 039	130 041	1 522 114
1976	87 726	—	87 726	1 636 990
Total	373 481	414 995	788 476	10 008 615

[a] Based on WHO financial records and SME/78.13, Government of the Sudan.
[b] Excluding the cost of 16 635 000 doses of vaccine.

provinces in the northern region. By that time it was hoped that the civil war in the southern provinces would have ceased, permitting operations to be conducted there. This initial vaccination of the population of the central provinces could help to ensure high levels of immunity in the agricultural areas, which received large numbers of migrant labourers, and thus serve to prevent the possible spread of smallpox to the northern provinces. However, little attention was given to the development of a reporting system or of a mechanism for the investigation of suspected cases.

WHO support was greater than during the earlier campaigns (Table 18.16) and this time included the services of a WHO adviser. Commitments of the Sudanese government were substantial and included a staff of 539 persons.

It was expected that transport and supplies would arrive in the autumn of 1967, thus permitting the programme to begin towards the end of the year. In 1967, however, war between Egypt and Israel closed the Suez Canal, and supplies and equipment had to be rerouted around the Cape of Good Hope. What with the longer journey and the chaos in shipping, the supplies did not arrive until early 1969. Meanwhile, freeze-dried vaccine was supplied by WHO for use by health service units. However, as in other countries, very few vaccinations were performed.

Smallpox is Reintroduced into the Sudan

The first of what were thought to be imported outbreaks occurred in Khartoum in July 1967, when 4 cases of smallpox were discovered whose source of infection was not identified. Because of the outbreak, a mass vaccination campaign was conducted in and near the city over a 3-week period, during which 717 904 persons were vaccinated. As expected, it was found that few children under 5 years (17%) had been vaccinated previously. In December, another outbreak of 5 cases occurred in Khartoum among Ethiopians from Eritrea, but smallpox did not spread among the now well-vaccinated population.

Beginning in February 1968, more outbreaks began to occur but little is known about their source or true magnitude. The importance of surveillance and containment measures was not then appreciated in the Sudan. In February, a patient from Kordofan Province developed smallpox in Khartoum, the probable source being vaguely identified as a market in Darfur Province. Smallpox was not known to be present in Darfur but no investigation was conducted. However, a mass vaccination campaign was organized in Kordofan during which 801 778 persons were vaccinated. In March, another case was recorded in Khartoum but its origins were not investigated.

WHO staff both in Geneva and in the Regional Office for the Eastern Mediterranean were alarmed by the occurrence of smallpox in a country which was thought to be free of the disease and anxiously sought additional information from the government and from the WHO smallpox adviser assigned to the Sudanese programme, but to no avail. In April 1968, cases began to be reported in Upper Nile Province as well. Dr Ehsan Shafa, the WHO Regional Adviser on Smallpox Eradication, was concerned about the situation and spent 2 months investigating outbreaks in this area and organizing mass vaccination campaigns. The first case was thought to have developed in December 1967, shortly after the infected person had arrived from Ethiopia. From there smallpox appeared to have spread to 10 other localities in Upper Nile Province. Subsequently, cases occurred in 3 areas which were 600 kilometres to the north, 1 area in Kassala Province and 2 in Blue Nile Province (Fig. 18.7), but their sources of infection were not identified. In all, 76 cases were detected in Upper Nile Province, the last on 16 May 1968. The discovery that the first known outbreak originated in Ethiopia, and that other outbreaks followed

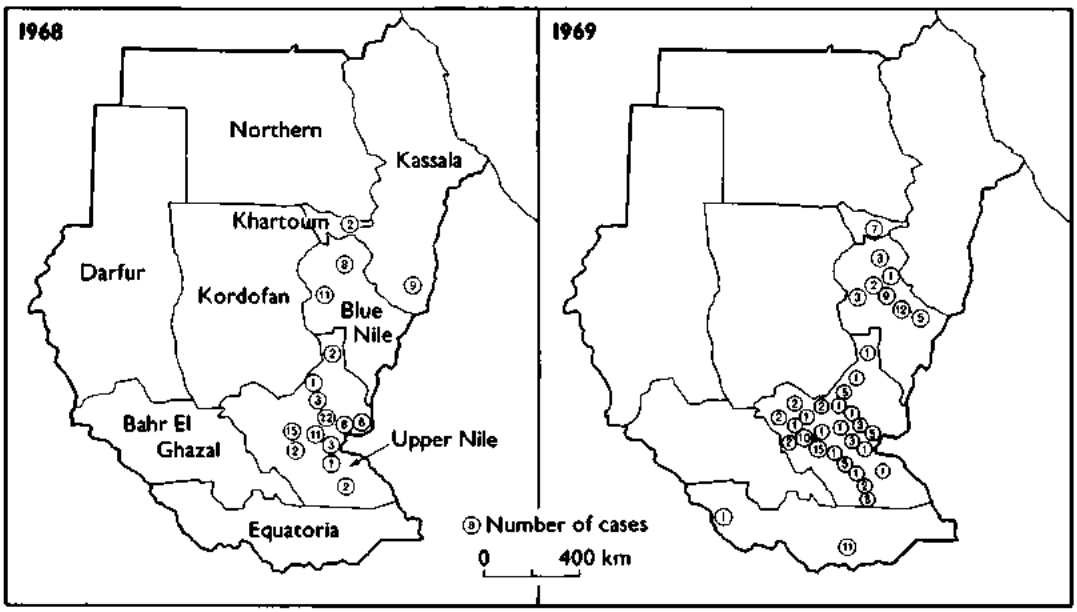

Fig. 18.7. Sudan: geographical distribution of reported cases of smallpox, 1968–1969.

in a temporal sequence moving from south to north, suggested that the series of outbreaks had originated from an importation with subsequent spread in a country otherwise free of smallpox.

To control the early 1968 outbreaks, mass vaccination campaigns were conducted in April and May: 452 256 persons were vaccinated in a single month in Upper Nile Province, 23 005 in Kassala Province, and 638 015 in Blue Nile Province—in all, more than a million people. Few vaccinations had been performed in Upper Nile Province during the 1961–1963 campaign, and the 1968 campaign reflected this. Of those aged 1–4 years, 72% received primary vaccination, as did 61% of the whole population. Primary vaccinees accounted for only 24% of the total in Kassala Province and for only 18% in Blue Nile Province. The last cases in these outbreaks were detected in June. Over the next 5 months, no further cases were reported (see Fig. 18.8).

The National Mass Vaccination Campaign is Launched, 1969

Considering the size of the country and the extensive movement of population in the Sudan, it was recognized that an effective mass vaccination campaign would be a challenge. Favouring its success, however, was the fact that the country's infrastructure of health services was among the best developed in Africa; maps and demographic data were available for most districts and council areas; and health units were widely dispersed. Moreover, a national vaccination campaign had been completed less than 5 years earlier. However, from its inception, the campaign experienced an array of problems. In mid-1968, 190 vaccinators were appointed, trained and posted to the central provinces. Within a short period, most resigned and returned to Khartoum, having found it difficult to cope with field conditions and having encountered resentment by the villagers, who were accustomed to locally recruited vaccinators. New staff were recruited and trained, of whom a greater proportion were from the provinces to be vaccinated, and in January 1969 field operations began.

The staff of 539 was substantially greater, in proportion to population, than in other African countries, in part because of the government's decision to provide BCG vaccine at the same time as the smallpox vaccine. Superficially, this appeared logical, but in practice it presented special problems. Smallpox vaccination in the Sudan was customarily performed by vaccinators proceeding from

house to house, the assembly of large numbers of people at collecting points not being well accepted in most areas. Because of this, jet injectors were not useful. Although smallpox vaccination, administered with the bifurcated needle, was well suited to house-to-house vaccination, BCG vaccination, which required the use of a needle and syringe, was not. Among the problems was that the needles had to be flamed after each inoculation and the syringes repeatedly refilled from the vaccine vial. Accordingly, BCG vaccine was customarily administered at assembly points. To the smallpox staff, it appeared impracticable to try to combine a house-to-house vaccination campaign with one which called for the gathering of children at a collecting point, but the government, supported by the WHO Regional Adviser for Tuberculosis, decided on the combined programme. Unfortunately, the operational problems were never resolved.

For the campaign, 30 vaccination units were constituted, approximately 10 for each of 3 provinces (Blue Nile, Darfur and Kordofan), each unit comprising 6 smallpox and 3 BCG vaccinators plus supervisors. The units moved systematically through the province. The smallpox vaccinators went from house to house; the BCG vaccinators worked at a collecting point, vaccinating those up to 20 years of age. Each group prepared a separate set of records listing the name of the head of each household, the number of residents by age group and the number of vaccinations performed. Thus, two sets of forms were prepared in each village; no effort was made to reconcile them and, in fact, the records were not subsequently used either in assessment or in follow-up vaccination.

The plan for assessment of vaccination coverage and take rates was likewise inefficient. It called for a separate assessment team to examine one-quarter of those residing in 50% of the villages after 1 week. This involved much more travel and manpower than the standard plan proposed in the 1967 WHO *Handbook for Smallpox Eradication Programmes in Endemic Areas* (SE/67.5 Rev.1), which suggested that 5–10% of the villages should be assessed.

Progress was slow. Smallpox vaccinators averaged only 25–35 vaccinations a day in 1969 and 40 a day in 1970. Those performing BCG vaccinations averaged somewhat less than half this number. Overall, productivity was one-tenth to one-third that of other programmes in Africa.

Recurrent Epidemic Smallpox, December 1968

While national and WHO staff struggled with the logistics of initiating the vaccination campaign, cases of smallpox once again began to be reported in late December 1968 in Upper Nile Province. A surveillance team had not yet been constituted and so 2 WHO staff members were again sent temporarily to the Sudan to investigate. From their observations, it was apparent that smallpox had reestablished itself in the country. The initially reported cases had occurred in villages near the Ethiopian border. The outbreak had spread westwards and northwards just as had happened earlier in 1968. However, careful epidemiological investigations suggested that this was not an importation from Ethiopia followed by localized spread, but rather the spread of smallpox from a number of endemic areas within the Sudan itself (*Wkly epidem. rec.*, 1969b). By the end of April 1969, the team had documented 119 cases in 4 provinces—Upper Nile, Blue Nile, Equatoria, and Khartoum. The beginning of the outbreak coincided with the beginning of the harvest season, when large numbers of seasonal workers began to travel from Upper Nile and Equatoria by boat, truck, train and on foot. Most of the cases were detected in special camps established for seasonal workers and at check-points for those in transit. It was clear that there were many more cases in villages, some in the southern areas afflicted by civil war, but in the absence of an organized reporting system, they were not being notified. The cases were of the mild variola minor type, only 3 deaths occurring among 119 patients. (These deaths are not recorded in the official figures given in Table 18.14.) Many patients were able to travel even when ill and thus readily disseminated the disease. The fact that half of all the cases were in persons over 15 years of age and that more men than women were affected (Table 18.17) reflected the spread of smallpox primarily among migrant labourers.

The investigators recommended that a surveillance programme should be established and a special campaign mounted to vaccinate seasonal workers in and *en route* to their camps. They believed that little could be done to vaccinate those in the southern provinces, but they reasoned that if the seasonal workers were well immunized, vaccinial immunity in sparsely settled rural areas of the south would

Table 18.17. Sudan: number of reported cases of smallpox, by age group and sex, January–April 1969

Age group (years)	Male	Female	Total	% of total for all ages
<1	2	1	3	3
1–4	14	13	27	24
5–9	7	7	14	12
10–14	5	7	12	10
⩾15	38	21	59	51
Total	66	49	115	100

be increased and, conceivably, the disease might die out.

The recommendations were not implemented but, as during the preceding year, the number of reported cases diminished; between the beginning of June and the end of November 1969, only 2 cases were notified (see Fig. 18.8).

Major Epidemics Begin, 1970

In Upper Nile Province 2 cases were reported in December 1969, 3 cases in January 1970, and 124 in February. Smallpox was also introduced into the northern Sudan from Ethiopia. Steadily the disease spread across the country to infect all but Darfur Province. In June 1970, a central surveillance team was appointed under the direction of Dr Sulieman, and by the end of the year, 1051 cases had been documented; most were detected by the surveillance team. Interestingly, adult cases continued to predominate, 55% being in persons over 15 years of age.

The vaccination campaign continued to progress slowly, its pattern of operation unchanged, as neither Sudanese nor WHO staff seemed able to devise an alternative operational approach. Continuing assessment showed that when vaccination had been completed in an area, consistently more than 85% and usually more than 95% of those under 5 years of age had a smallpox vaccination scar. Among older children and adults, the proportions were even higher, reflecting past vaccination efforts. BCG vaccination coverage, however, was usually in the range of 60–75% and sometimes lower. WHO regional smallpox eradication staff urged that BCG vaccination should be suspended until smallpox transmission had been interrupted, but, to the government, the policy of providing two vaccines simultaneously remained an attractive one. The smallpox eradication staff turned for advice to the WHO Regional Adviser for Tuberculosis, who had originally advocated the plan. Unhelpfully, he concluded in his report: "Certainly, the least attractive approach would be to continue the *status quo*, that is smallpox vaccination from house to house and BCG vaccination at collecting points." He offered no alternative plan, concluding only with the advice: "Whatever the final solution, one should test-run the various approaches as envisaged ... and select the most promising one."

By June 1970, 18 months after the programme had begun, only 5.3 million persons had been vaccinated, an estimated 68% of the population in the 3 provinces in which operations had been expected to be completed during the first year of the programme. Outside of these 3 provinces, the number of vaccinations recorded was equivalent to 5% or less of the population.

At the end of August, the programme stopped altogether when cholera cases were detected in the Sudan and the Ministry of Health decided to assign the teams to conduct a mass cholera vaccination campaign. Cholera vaccine offered little protection but was widely used nevertheless in many countries at that time. During November, no smallpox or BCG vaccinations were performed and, for many months thereafter a considerable number of teams and vehicles continued to be used for the administration of cholera vaccine. During December 1970, the smallpox–BCG vaccination campaign was gradually resumed but, as was noted in the populous Blue Nile Province, many villagers had left by that time to pick cotton. Entire villages were found empty or with very few residents. Vehicles were in critically short supply, some having been irreparably damaged by the bad roads, some remaining with cholera vaccination teams and some having been diverted to other uses by the Ministry of Health. In March 1971, the mass campaign finally concluded in the central provinces, more than 2 years after it had begun. The number of vaccinations reported to have been performed during 1969–1970 was greater than in 1968 (Table 18.18), but not commensurate with that expected of a staff of more than 500.

The vaccination campaign shifted to the northern provinces in 1971 and coincidentally the surveillance programme—such as it

Table 18.18. Sudan: number of reported vaccinations, 1968–1975

Year	Number of vaccinations
1968	1 967 450
1969	3 404 587
1970	4 871 573
1971	2 376 038
1972	2 268 142
1973	1 944 700
1974	1 121 693
1975	942 068

was—ceased when Dr Sulieman was reassigned to organize the vaccination campaign in Kassala Province. The WHO regional office replaced the WHO smallpox adviser by another adviser who, like his predecessor, was an ardent proponent of mass vaccination, with no understanding of the importance of the surveillance–containment strategy despite intense efforts at persuasion by the WHO regional office and Headquarters staff. The contributions of these advisers to the field programme were further compromised by the fact that neither travelled frequently out of Khartoum.

By the autumn of 1971, smallpox transmission in Africa had been interrupted in all but 3 countries: Ethiopia, in which the programme had only just begun; Botswana, which had become reinfected that summer following an importation from South Africa; and the Sudan, whose programme was then in its fifth year. Cases in the Sudan were being reported from all provinces, although of greatest concern were the 3 in the south, in which no formal smallpox programme activities were being conducted and from which 55% of all cases were then being reported. Some cases in Uganda were also traced to this area.

To assess what, if anything, could be done, Dr Shafa, then assigned to the WHO Smallpox Eradication unit in Geneva, visited the southern provinces in late October. He determined that movement out of the main towns was restricted but convoys regularly travelled to various areas, including the health establishments, which, for a population of 2.5 million, were quite numerous (Table 18.19). None held stocks of smallpox vaccine. None reported smallpox cases regularly, but all stated they could readily do so by utilizing police and army radio. It was apparent that vaccination and the investigation of outbreaks were impossible in rural areas, but

D. P. FRANCIS

Plate 18.7. A provincial smallpox eradication office in the northern Sudan in September 1973. By that time the programme had been reorganized primarily as a surveillance operation.

Table 18.19. Southern Sudan: number of health establishments, by category and province

Province	Hospitals	Dispensaries	Dressing stations
Upper Nile	5	38	42
Equatoria	5	19	38
Bahr El Ghazal	7	12	54
Total	17	69	134

much could be done in the main towns and in districts adjacent to health units. Learning that a year earlier cholera vaccine had been successfully administered throughout the area with the help of police and army personnel, Dr Shafa proposed that vehicles, vaccine and other necessary supplies should be sent to the south, and that personnel from the southern provinces, then working in the mass vaccination campaign in the north, should be transferred to staff surveillance teams. Vaccine was sent to the south but the smallpox eradication programme leadership remained preoccupied with the mass vaccination campaign in the north and little else was done.

D. P. FRANCIS

Plate 18.8. Omer Sulieman (b. 1940) organized a central surveillance team in the Sudan in June 1970 which was disbanded in March 1971, when mass vaccination began in the northern provinces. He re-established a surveillance programme in January 1972 and transmission ceased by the end of the year. Subsequently, he was recruited by WHO and served as smallpox eradication adviser in Pakistan.

The Initiation of an Effective Surveillance–Containment Programme, 1971

As viewed by WHO Headquarters staff, the critical problem for the Sudan lay in establishing an effective surveillance and containment programme. For this to be done without the support of senior programme staff or the WHO adviser seemed unlikely. Nevertheless, more in despair than in hope, it was agreed that a special seminar on surveillance would be conducted in December 1971 for physicians and senior sanitary inspectors in each province. Hope was expressed that some way might be found for Dr Sulieman again to be given responsibility for supervising surveillance activities. Replacement of the WHO adviser was proposed but the WHO regional office disagreed. However, the addition of a

Vaccination Conducted by the Anyanya Resistance Movement

In 1970, WHO staff in Geneva were asked for vaccine by representatives of the Anyanya Resistance Movement, the rebel forces in the southern Sudan. They denied that smallpox was present in the area but were concerned that epidemics might occur. When asked how they could transport the vaccine, they indicated that they regularly took supplies north by road from Kampala, the capital of Uganda, and from there travelled on foot for 7–10 days into forest areas of the southern Sudan. Government staff could not reach these areas but, officially, WHO could provide vaccine only to Member governments. It was a quandary because, clearly, it was in everyone's best interest for this area to be better protected.

The dilemma was resolved by transferring vaccine to leaders of the resistance movement and recording the amount as "lost from inventory". Whether or not it was used properly was unknown until after March 1972, when the civil war ended. Sudanese staff found on investigation of outbreaks that the Anyanya had conducted quite extensive vaccination campaigns although, as they pointed out, many persons remained unvaccinated.

Plate 18.9. Migrants crossing the White Nile River at Juba in the southern Sudan. Civil war in the southern provinces resulted in a flow of refugees into Uganda and Zaire, who nevertheless frequently returned to trade or to visit relatives. They were the source of many importations of smallpox into Uganda between 1969 and 1972.

second WHO adviser was accepted provided that WHO Headquarters could find the necessary funds.

To the surprise of all concerned, the December seminar proved to be the turning-point. As Dr Sulieman later observed, he appreciated for the first time how important surveillance and containment really were. Following the seminar, and over the objections of the WHO adviser, he resumed responsibility for the surveillance programme. With a remarkably imaginative and energetic group of public health officers serving as directors of provincial surveillance teams, he began to strengthen reporting, to search for cases and to investigate outbreaks throughout the central and northern provinces. Many outbreaks were discovered and contained. Where resistance to vaccination was encountered, vigorous measures were taken. For example, cooperation was poor in one village in Kordofan; the police surrounded it before sunrise, and vaccinators moved from house to house and room to room, searching and vaccinating. By April, virtually all cases were occurring among travellers from the south, and in June the last cases were detected in the central and northern provinces.

At the end of March 1972, the government and the southern rebel forces—the Anyanya Resistance Movement—signed a treaty of reconciliation. In May, Dr Sulieman transferred his headquarters, including personnel and vehicles, to Bahr El Ghazal to begin work in the south. The rainy season was under way and travel in rural areas was difficult; in some it was impossible until October. In the latter areas, this period was used to construct detailed maps of the routes followed by migratory workers. An order was issued requiring all health units to report cases weekly; all chiefs, subchiefs, police stations, schools, forest and road workers were contacted and asked to report cases to these centres. Work was begun with 44 health staff who undertook a rapid house-to-house search throughout accessible areas.

Vaccination was performed only where outbreaks were encountered. By means of a scar survey, staff discovered that in most towns and villages along the way, 90% or

more of the population had been vaccinated. The cases found in these areas were generally on the periphery of towns and were quickly contained. However, many persons had moved deep into the jungle during the war. There, vaccinial immunity was far lower and rumours of outbreaks were difficult to trace. Accordingly, former Anyanya military personnel were recruited and given bicycles to search for cases in remote areas - -areas well known to them. Returning refugees were vaccinated at resettlement camps; health units throughout the 3 provinces were given supplies of vaccine and instructed to vaccinate both those attending centres and others living nearby. In June 1972, the programme was extended to Equatoria and Upper Nile Provinces. By the end of September 1972, 17 outbreaks had been discovered in Bahr El Ghazal, 10 in Equatoria and 1 in Upper Nile. Surprisingly, the largest of these consisted of only 25 cases. The cooperation of those living in the area was illustrated by the fact that in Equatoria, the last 2 outbreaks were reported by a villager and a chief who, respectively, walked 45 and 70 kilometres to report cases. In October, the rains stopped and the systematic search was extended throughout the rural areas. Teams travelled on northward-bound river steamers to search for cases and to vaccinate embarking passengers, and other check-points were established. Fifty medical students from the School of Medicine in Khartoum joined the programme, working in teams with vaccinators to search for outbreaks and to contain them. Only 5 additional outbreaks were discovered in Bahr El Ghazal Province and 1 in Upper Nile Province, although numerous patients were found who had experienced the onset of illness many weeks previously. Fig. 18.8 shows the number of cases of smallpox by week of report and by week of onset. Interestingly, the last case was discovered on 17 December 1972 in a village called "Malek", which is the local name for smallpox. One additional patient who had been infected in Ethiopia developed smallpox on 23 December in northern Kassala Province but he was the last.

On Dr Shafa's recommendation, a former operations officer from the Ethiopian programme, Mr James Lepkowski, and a former medical officer from the western Africa programme, Dr Donald Francis, were assigned by WHO to Juba in Equatoria Province in November 1972 and January 1973 respectively. A thorough systematic search for cases was organized throughout the southern provinces and subsequently in areas bordering on Ethiopia. It seemed inconceivable that transmission had been stopped throughout such a vast area, in which, less than a year before, smallpox had been reported from all provinces. However, no cases could be found (WHO/SE/73.60, Lepkowski et al.; WHO/SE/74.67, Bassett et al.). During the course of a single year, Dr Sulieman had brought order out of chaos and had succeeded in stopping transmission before additional manpower from WHO had had time to arrive on the scene. In September 1973, a village-by-village search was conducted throughout the country, but again no cases were found.

Smallpox remained widely prevalent in Ethiopia, however, and, as previously noted, many people travelled between the Sudan and Ethiopia. Special surveillance units were posted to migrant labour and refugee camps,

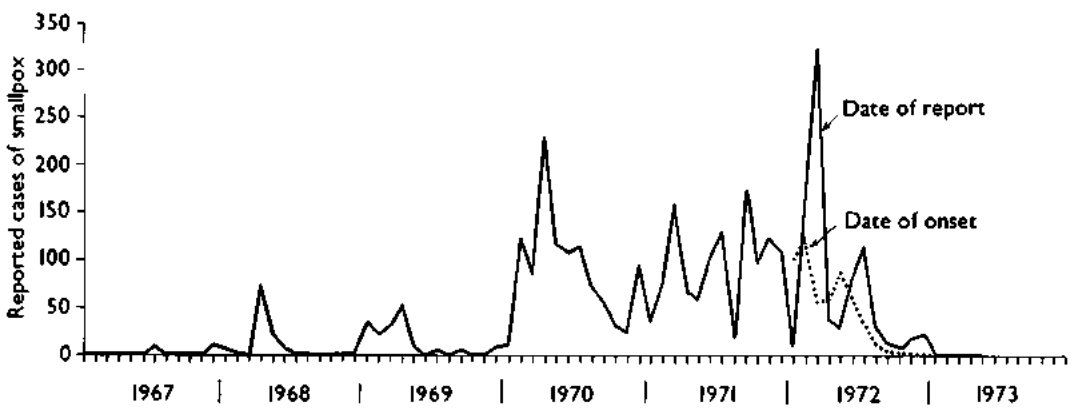

Fig. 18.8. Sudan: number of reported cases of smallpox, by month, 1967–1973, with cases plotted according to week of report and week of onset for 1972.

Plate 18.10. Donald P. Francis (b. 1942), an epidemiologist, was the WHO smallpox eradication adviser in the Sudan from January 1973, arriving just after the occurrence of the last known case in the country. With the Sudanese staff, he helped to organize a national surveillance system to protect against the effect of importations of smallpox from Ethiopia.

search workers were assigned to travel on the river steamers and special search teams covered the border areas. Many rumours of cases were received, but none proved to be smallpox. In September 1972, during a seminar in Addis Abeba, it was proposed that Sudanese and Ethiopian teams should be granted permission to cross the border without hindrance when undertaking search operations. Both governments agreed and, thereafter, Sudanese teams investigating rumours of cases, sometimes at the request of Ethiopian programme officers, travelled far into Ethiopia. In November 1973 and in March 1974, the teams undertook special search and vaccination programmes over extensive areas, difficult of access, in Ethiopia.

Table 18.20. Sudan: results of vaccination scar survey, by age group and province, 1975–1976

Region and province	Number examined	Percentage with vaccination scars			
		<1 year	1–4 years	5–14 years	⩾15 years
Northern region:					
Kassala	15 657	86	84	97	94
Central region:					
Blue Nile	12 047	55	72	90	90
Darfur	6 789	67	60	82	81
Kordofan	601	78	88	91	95
Southern region:					
Upper Nile	3 148	29	75	77	94
Equatoria	2 930	77	88	82	98
Bahr El Ghazal	6 438	15	25	75	71

The level of vaccinial immunity attained in the Sudan had been assessed in the central and northern provinces and found to be uniformly high, although doubt was expressed whether the surveys had been properly conducted. Not until 1975-1976 was a reliable cluster sample survey performed. It was found that coverage, in general, was high except in Bahr El Ghazal, in which systematic mass vaccination had not been conducted (Table 18.20).

The age and sex distribution of cases in the Sudan in 1970 was most unusual in that nearly half of all cases for which data are available were in adults, of whom 60% were male (Table 18.21). A large proportion of the recorded cases that year occurred among adult migrants coming from endemic areas in the south and in labour camps. As the disease continued to spread in the north, larger proportions of children were affected. Finally, in 1972, as cases in southern endemic areas were investigated, more cases were found in children, and the age distribution more nearly approximated to that found in other endemic areas: 15% of patients were under 5 years of age, and 48% were aged 5–14 years.

Table 18.21. Sudan: number of reported cases of smallpox, by age group and sex, 1970–1972[a]

Age group (years)	1970				1971				1972			
	Male	Female	Total	(%)	Male	Female	Total	(%)	Male	Female	Total	(%)
<1	8	8	16	(2)	22	12	34	(3)	11	14	25	(5)
1–4	77	64	141	(15)	116	90	206	(19)	45	11	56	(10)
5–14	112	140	252	(27)	206	174	380	(36)	174	91	265	(48)
⩾15	337	178	515	(56)	259	188	447	(42)	114	92	206	(37)
Total			924	(100)			1 067	(100)			552	(100)

[a] Data not recorded for 127 cases in 1970, 74 cases in 1971, and 275 cases in 1972.

Investigation of a Suspected Case

The problems of travel are well illustrated by extracts from a report of the investigation of a case by Dr Satnam Singh, a WHO epidemiologist in the Sudan. On 10 September 1975, the smallpox programme office was notified of a suspicious rash in a 40-year-old woman seen at a dispensary in the village of Geissan, on the border of the Ethiopian region of Gojam, where many cases of smallpox had been occurring. Because of drought in their own country, many Ethiopians had begun to visit Geissan to obtain sorghum. The report stated that the patient had been isolated and 12 family members vaccinated as well as 980 residents and visitors in the village. The report had been delivered to the nearest telegraph station, Damazien, 156 kilometres away, after a 5-day journey on foot. The telegraph line being out of order, it was not until 9 September that the provincial medical officer received the message. He then telephoned in the report.

A sanitarian, Mr Abdul Gadir El Sid, joined Dr Singh on the first available flight to Damazien on 13 September. There the Assistant Commissioner provided them with a 4-wheel-drive all-terrain vehicle (a UNIMOG) and a 4-wheel-drive army vehicle for a trip expected to take 10–15 hours. They were accompanied by smallpox eradication workers and a few army personnel. As Dr Singh wrote: "From the moment we left Damazien, we realized it would be difficult to traverse the water-logged muddy track overgrown with 12-foot-high grass. Regularly, the army vehicle, despite its more powerful engine, got stuck in the sticky mud and had to be pulled out manually, aided by cables attached to the UNIMOG. The multiple running streams (*khors*) that criss-crossed the track along the west bank of the Blue Nile caused additional delays. Some required reconnaissance on foot above and below the track to find a suitable crossing and the same was done when the regular track was waterlogged for long stretches. Detours were made through the tall grass fields and bushes. After one and one-half days' travel and a one-night halt, we had only covered a quarter of the distance and found ourselves with only the UNIMOG operational—the other vehicle having been irreparably damaged. It was decided that a few should return to Damazien to mount another expedition including a tractor.

"The return journey to Damazien was worse for it had rained in the meantime. After a one-night halt in a village, we reached Damazien at 9:00 p.m. on 16 September . . . and on the 18th we started for Geissan with one tractor, the same UNIMOG and a relatively new army vehicle with a mechanic and spare parts.

"To have a tractor was a boon. The vehicles when stuck were pulled out quickly. In the meantime, however, more rain fell and in consequence more swollen rivulets and *khors* had to be crossed. On the 19th, we had to abandon the army vehicle and pushed ahead with the UNIMOG and the tractor. In spite of the rainstorm, the river was only waist deep but with a fast current. Our vehicles forged through with manual help from the villagers. The rest of the journey was uneventful except that the terrain near Geissan is so hilly that in a few places there was a real danger of the vehicles turning over into the valley. We got a rousing welcome from the residents of Geissan, a community of 1500 persons, when we reached there at 8:30 p.m. on the 21st.

"The patient's rash had healed, but clinical and epidemiological examination clearly indicated that it was a case of chickenpox.

"We began our return journey on 24 September. The return trip was even slower as more rain had fallen. On 25 September, we reached a *khor* so heavily flooded that several days' wait would be required for the waters to recede. The writer and Abdul Gadir decided to complete the trip by boat. We obtained a small leaky fishing canoe and paddled down the flooded Blue Nile endeavoring to avoid the larger, frequent whirlpools. After 4 hours, we pulled ashore at a village to camp for the night and there were able to get a wooden boat with motor which took us to Damazien. On the following day, 27 September, 14 days after arrival, we took the once-weekly air flight back to Khartoum."

During most years and in most age groups cases were more frequent in males than in females. For adults, this was to be expected because the migrants were more often males. For younger age groups, there is no ready explanation for the sex differential. However, the data must be interpreted with caution because outbreaks were not thoroughly investigated until 1972 and, even then, investigation in the tropical forest areas was by no means complete and, in some areas, cases remained undetected because they were hidden from the investigators.

CONCLUSION

The smallpox eradication programmes in the Sudan and Zaire, two of Africa's largest countries, present a study in contrasts. When the programme began in Zaire, smallpox was highly endemic. The population was poorly vaccinated, and its professional staff and health infrastructure were at an early phase of development. Conversely, the Sudan in 1967 was free of smallpox, vaccinial immunity in the central and northern provinces was high and the country's health structure was comparatively advanced.

Both countries endeavoured to execute nation-wide vaccination campaigns employing both BCG and smallpox vaccines, the first programmes to administer the two antigens simultaneously. It was expected that there might be operational difficulties in conducting a time-limited mass campaign which required field activities to accommodate the administration of smallpox vaccine to the entire population and the administration of BCG vaccine to children and adolescents. WHO smallpox staff argued that it would be preferable to begin field operations using only one antigen, and to add the second after the programme had become established. Those responsible for tuberculosis control were anxious that BCG vaccination should be incorporated in the programme from the outset, arguing that to administer two vaccines entailed little more in cost or effort than to administer one. This view prevailed.

As was foreseen, both programmes did experience substantial problems in administering the two antigens simultaneously. Zaire, however, was soon able to resolve the difficulties by using jet injectors for both vaccines and to administer them to groups assembled at collecting points. In little more than 3 years, a country-wide programme had been completed with a staff which, at its maximum, numbered 234 persons. In the Sudan, the assembling of the general population at collecting points was not well accepted, thus precluding the effective use of jet injectors. Smallpox vaccination was therefore conducted from house to house with the bifurcated needle, while BCG vaccine was administered by needle and syringe to children at collecting points—a system that never worked well. Despite a staff of more than 500 persons, the programme proceeded slowly and, in fact, was terminated before vaccination had been completed throughout the country.

Acceptance and understanding of the concept of a national programme for the surveillance and containment of outbreaks likewise differed in the two countries. In the Sudan, as was the practice in other countries with a comparatively well developed infrastructure of health services, provincial and district health officers had primary responsibility for disease control. These medical officers differed greatly in their abilities, their understanding of epidemiology and their perception of priorities and, with no national surveillance unit to provide support and guidance, most controlled such smallpox outbreaks as were discovered in the traditional manner—by mass vaccination. Efforts to improve reporting and to investigate outbreaks to ascertain the sources of infection were uncommon. The belief that no special national surveillance programme was required was reinforced by the fact that the Sudan had succeeded in interrupting smallpox transmission in 1963. In the absence of a national surveillance programme, the disease, following its reintroduction in 1970, spread to almost all parts of the country. When a surveillance programme commenced in 1972, transmission was stopped within 12 months.

By contrast, in Zaire, in which the health structure was less sophisticated and not so well established, the concept of a national surveillance programme was more readily accepted. This proved to be the experience in many of the less well developed countries. Although the establishment of an effective surveillance programme was greatly delayed, owing to the lack of experienced personnel, the programme in Zaire succeeded in interrupting transmission some 18 months before that in the Sudan.

The contributions of WHO and other international agencies were critical to the success of both programmes, but in neither country were they as effective as they might have been. In Zaire, transmission might have been interrupted far sooner had the promised WHO resources been provided in a timely manner; in the Sudan, the assignment of effective advisers might well have helped to prevent the re-establishment of smallpox.

Whatever the problems, the attainment of eradication was a notable achievement in both countries, given their size, the formidable difficulties of transport and communication and the persistence of civil disorder.

CHAPTER 19

EASTERN AFRICA: KENYA, UGANDA, UNITED REPUBLIC OF TANZANIA, RWANDA AND BURUNDI

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INTRODUCTION

This chapter describes the development of smallpox eradication programmes in 5 contiguous countries of eastern Africa—Burundi, Kenya, Rwanda, Uganda and the United Republic of Tanzania[1] (Fig. 19.1). In 1970 their combined population amounted to 42 million and their total land area to 1 818 000 square kilometres. In comparison, adjacent Zaire to the west had half as large a population in 1970 but an area 25% greater.

The infrastructure of transport and communication services was better developed than in the countries of western and central Africa; moreover, government and private health centres, clinics, dispensaries and hospitals were more numerous. Vaccination, with liquid vaccine, had been practised more or less extensively throughout most parts of these countries for more than 50 years, most vaccinations being given when outbreaks of smallpox occurred. Some health facilities offered vaccination to any patients attending them, but the vaccine was generally stored at room temperature and its potency was therefore presumably low or nil.

Among the many health problems in these countries, smallpox in the early 1960s had not been of high priority except in Tanzania. Epidemics of variola major had occurred in previous decades but, more recently, in all countries except Tanzania, variola minor with a low case-fatality rate prevailed. For example, during the period 1961–1965, 1182 cases with only 6 deaths were reported from Kenya, and between 1961 and 1964 Uganda recorded 1960 cases and 4 deaths. However, Uganda in 1965 and Kenya in 1966 began to

[1] The United Republic of Tanzania was formed in 1964 by the union of Tanganyika, Zanzibar and Pemba. Although its official name is used elsewhere in this book, it is, for brevity, referred to as "Tanzania" in the text and tables of this chapter. The islands of Zanzibar and Pemba experienced no smallpox and conducted no special eradication programme.

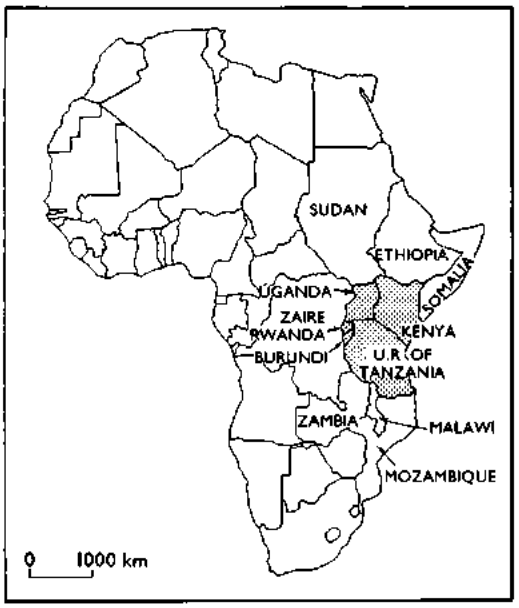


Fig. 19.1. Eastern Africa and adjacent countries.

experience an increasing number of deaths due to smallpox and consequently took a greater interest in controlling the disease. In Tanzania, a more severe form of smallpox had been prevalent, with recorded case-fatality rates of 5–7%. Even so, the problem was not large when viewed against the greater threats posed by malaria, tuberculosis and several other infectious diseases. Vaccination campaigns, however, were an integral part of public health activities because of the fear of recurrence of epidemics of the virulent variola major. With substantial commerce and travel between eastern Africa and Asia and the generally held belief that severe variola major prevailed elsewhere in Africa, there was reason to maintain adequate levels of vaccinial immunity.

After 1967, when the Intensified Programme began, all 5 countries agreed to undertake eradication programmes which would include systematic national vaccination campaigns employing, for the first time, freeze-dried vaccine of acceptable quality. WHO provided each country with advisers, all the requisite transport, equipment and supplies (including vaccine) and reimbursed the governments for the costs of petrol and vehicle maintenance. The countries made available a small cadre of national personnel, but little else. Each conducted effective national smallpox vaccination campaigns, which, in Kenya, Rwanda and Tanzania, were carried out in conjunction with the administration of BCG (antituberculosis) vaccine to children under 15 years of age.

Smallpox vanished quickly, transmission being interrupted by the end of 1970, well before the systematic vaccination campaigns reached most areas and, indeed, before effective programmes of surveillance and containment had been developed. After 1970, importations from the Sudan occurred along Uganda's northern border, and importations from Ethiopia and Somalia along Kenya's north-eastern borders. The outbreaks were all in sparsely populated areas; none resulted in large numbers of cases or persisted for long periods.

The mass vaccination campaigns differed somewhat in character from one country to the next, as each was adapted to the nature of the health services and the political structure of the country concerned. Information about the epidemiological characteristics of smallpox in eastern Africa is scarce, however, because little was done to improve the national reporting systems or systematically to investigate suspected cases until after 1970, when transmission had been interrupted.

The rapidity and ease with which smallpox transmission was interrupted in these countries, as well as many others in Africa, were surprising. At the time, the situation served to engender an unwarranted confidence that smallpox eradication could be readily achieved with only a modest incremental investment of resources, even in programmes in which performance was marginal. In Africa itself--notably in Ethiopia, Somalia and the Sudan—this belief later proved to be unfounded.

SMALLPOX CONTROL ACTIVITIES BEFORE 1969

In 1967, when the Intensified Smallpox Eradication Programme began, the countries of eastern Africa reported a total of only 2221 cases (Table 19.1). In a population which then numbered almost 38 million, this figure was not large. Moreover, the number of recorded cases was diminishing rapidly, from 5607 in 1965 to 4163 cases in 1966. Of the 5 countries, only Rwanda reported no cases whatsoever during the period 1966–1968 but it was provisionally categorized as an endemic country, since it was difficult to believe that a

Table 19.1. Eastern Africa: population and number of reported cases of smallpox, 1965–1977

Year	Number of cases				
1970 population (thousands)	Kenya	Uganda	Tanzania	Rwanda	Burundi
	11 290	9 806	13 513	3 718	3 456
1965	276	1 351	2 762	5	1 213
1966	159	614	3 027	[a]	363
1967	153	365	1 629	[a]	74
1968	87	55	455	[a]	301
1969	14	9[b]	117	107	108
1970	0	2[b]	32[c]	253	197
1971	46[b]	19[b]	0	0	0
1972	0	16[b]	0	0	0
1973	1[b]	0	0	0	0
1974	3[b]	0	0	0	0
1975	0	0	0	0	0
1976	1[b]	0	0	0	0
1977	5[b]	0	0	0	0

[a] No cases officially recognized.
[b] Imported cases.
[c] Including 23 cases resulting from importations.

country completely surrounded by heavily infected areas could be free of smallpox. Not until 1969 was it learned that it was government policy to report only cases that were confirmed by laboratory examination. Because no specimens were examined, no cases were reported.

Vaccination was provided routinely in all countries, the number performed annually being equivalent to about 10–20% of the population (Table 19.2). Undoubtedly many of the vaccinations were unsuccessful because of the use of vaccine that was subpotent at the time of administration. Kenya, Tanzania and Uganda used liquid vaccine produced at the Medical Research Laboratory in Nairobi or at the Lister Institute, England. Although usually stored under refrigeration in the capital city, the vaccine was exposed to ambient temperatures during shipment and rarely refrigerated at any of the intermediate distribution points or in health centres. This was a problem, because liquid vaccine becomes inactive within 3 days or less at ambient temperatures when it is not refrigerated. No data are available regarding the proportion of successful vaccinations because vaccinees were not examined to determine whether their vaccinations had taken. Until 1965, Rwanda and Burundi also used liquid vaccine, produced at a laboratory in Rwanda or imported from Belgium. In 1965, the Rwanda laboratory began producing a reasonably satisfactory freeze-dried vaccine, but the vials in which it was distributed were so large that the amount of vaccine each contained was sufficient, after reconstitution, for 600 doses or more. This was not much of an improvement, because freeze-dried vaccine, after reconstitution, loses its potency within 24 hours unless it is refrigerated, and few health centres had refrigerators which functioned properly. Rarely did any health unit have cause to vaccinate more than a few persons a day but the staff continued to use the reconstituted vaccine until each vial was empty. In 1968, for example, a WHO smallpox eradication adviser observed at a hospital in Rwanda that a vial containing vaccine reconstituted 3 months earlier was still in use.

In each of the countries, mass campaigns were conducted from time to time in specific areas when epidemics occurred. For such campaigns, vaccine was shipped to the field direct from the laboratories and was more likely to have been of adequate potency at the time of administration than vaccine which had been kept for weeks or even months at health centres. Only one country-wide mass vaccination campaign—in Uganda—had been carried out since the 1950s. In 1965, the number of reported smallpox cases and deaths in Uganda increased. The Ministry of Health, fearing epidemic variola major, launched a national campaign. Between August 1965 and February 1966, 7.5 million persons were vaccinated, a total equivalent to more than 90% of the country's population at the time. The cost of vaccine alone, most of which was purchased from the United Kingdom, amounted to more than US$200 000. A survey conducted by Ladnyi in 1966 revealed vaccination scars in 88% of children in primary

Table 19.2. Eastern Africa: number of reported vaccinations and proportion of population vaccinated each year, 1967–1973

Year	Number of vaccinations given (thousands)											
	Kenya				Uganda		Tanzania		Rwanda		Burundi	
	By mobile teams	By health units	Total	% of population	Number	% of population	Number	% of population	Number	% of population	Number	% of population
1967	–	1 179	1 179	12	959	11	2 451	20	467	14	262	8
1968	–	1 516	1 516	14	665	7	2 123	17	287	8	300	9
1969	331	948	1 279	12	887	9	2 791	21	1 064	30	416	12
1970	4 462	1 574	6 036	53	8 500	87	3 864	29	2 293	62	1 817	53
1971	3 530	2 441	5 971	51	138	1	4 639	33	210	5	765	22
1972	2 158	686	2 844	23	171	2	2 604	18	80	2	30	1
1973	1 243	541	1 784	14	88	1	1 325	9	129	3	362	10

schools, but in only 61% of people attending clinics at 6 hospitals. The examination of 33 patients with smallpox revealed that 8 had been unsuccessfully vaccinated 1–3 months before. It was apparent that the campaign had been far less successful than the coverage might suggest.

The impression that a more severe form of smallpox had appeared in Uganda is borne out by the available records. Up to 1965, deaths from smallpox had been infrequent in Uganda, but in 1965 the case-fatality rate increased to nearly 5% and remained high until transmission was interrupted (Table 19.3). During the following year, the case-fatality rate in Kenya also increased, with both cases and deaths occurring primarily in areas adjacent to Uganda. Kenya, too, undertook a mass campaign—in Nyanza Province, which borders on Uganda. Between March and April 1966, 670 000 persons were vaccinated. In the same year, 500 000 people in Burundi and 6 million in Tanzania were vaccinated during mass campaigns.

From 1966 onwards, the case-fatality rates in Uganda and Kenya were characteristic of those observed with the African strain of variola major. This strain had been prevalent in neighbouring Tanzania and Zaire, from which it had presumably been introduced. Nothing can be said of the status of Rwanda or Burundi at this time, because no cases were officially recognized by Rwanda and deaths were not registered in Burundi.

AGREEMENTS TO UNDERTAKE ERADICATION PROGRAMMES

In October 1965, Ladnyi was assigned by WHO to Nairobi as an intercountry smallpox adviser in the eastern portion of Africa. He was responsible for providing advice on the development of smallpox eradication programmes to the 19 countries of eastern, central and southern Africa in WHO's African Region that lay to the south of the Sudan, Ethiopia and Somalia (which at that time all formed part of the Organization's Eastern Mediterranean Region). An epidemiologist based in Liberia was assigned similar functions in the western portion of Africa. The initiative by the Regional Office for Africa to provide regional smallpox eradication programme advisers antedated the decision of the Nineteenth World Health Assembly in May 1966 to allocate special

WHO

Plate 19.1. In Rwanda and throughout eastern Africa, mass vaccination had traditionally been used to control the spread of smallpox. Villagers willingly assembled at collecting points to be vaccinated.

funds for eradication; they were, in fact, the first WHO regional smallpox eradication staff to be appointed. Ladnyi immediately embarked on a series of visits to each of the countries, beginning in 1966, with Burundi, Kenya, Malawi, Tanzania, Uganda and Zambia.

At the start, he could do little except offer advice, since the resources allocated to the smallpox eradication programme by WHO were so limited. Moreover, because most countries did not consider smallpox an important problem, few were interested in developing programmes, or, indeed, were able to do so without special assistance.

The above-mentioned decision of the Nineteenth World Health Assembly to allocate funds for smallpox eradication from the Organization's 1967 regular budget made it possible to launch many national programmes. Surprisingly, however, except for those from Zaire and Zambia, no requests for assistance were received by WHO from any of the countries in central, eastern or southern Africa. Meanwhile, during 1966 and 1967, programmes throughout western

Table 19.3. Kenya, Uganda and Tanzania: number of cases of and deaths from smallpox, and case-fatality rates, 1961–1970

Year	Kenya			Uganda			Tanzania		
	Number of cases	Number of deaths	Case-fatality rate (%)	Number of cases	Number of deaths	Case-fatality rate (%)	Number of cases	Number of deaths	Case-fatality rate (%)
1961–1964	906	4	0.4	1 960	4	0.2	4 373	249	5.7
1965	276	2	0.7	1 351	63	4.7	2 762	213	7.7
1966	159	9	5.7	614	25	4.1	3 027	171	5.7
1967	153	18	11.8	365	24	6.6	1 629	50	3.1
1968	87	3	3.4	55	5	9.1	455	16	3.5
1969	14	0	0	9[a]	0	0	117	1	0.9
1970	0	0	-	2[a]	0	0	32	0	0

[a] Cases imported from the Sudan and Rwanda.

Africa began to develop with assistance provided by the USA (see Chapter 17). Smallpox eradication staff from WHO Headquarters asked the regional office to contact the eastern and southern African countries to ascertain their interest in developing eradication programmes. However, the regional office pointed out that, as a matter of policy, it responded only to requests for assistance initiated by the countries themselves. In part, this policy derived from the views of the Director-General of WHO. In meetings with his regional directors in 1966, he had urged extreme caution about imposing another mass programme on Member states, after the experience with malaria eradication. The regional directors, in turn, had conveyed this to the WHO representatives in the countries themselves. Because the Director-General regarded smallpox eradication as improbable, he believed that such a programme would only divert national resources from more important activities (see Chapter 10). The WHO smallpox eradication staff in Geneva, on the other hand, maintained that the decision to undertake global smallpox eradication had received the unanimous approval of the World Health Assembly; funds had been appropriated for this purpose and thus it seemed only reasonable to contact the endemic countries to assess their intentions and needs. To expect the African countries themselves to respond spontaneously to new programme directions seemed unrealistic. All were newly independent, beset with problems and struggling to bring order into chaotic bureaucracies. These arguments were, however, of no avail.

Ladnyi, as a member of the regional office staff, had his hands tied; there was little he could do to overcome the apparent impasse in the initiation of eradication programmes in central, eastern and southern Africa, without directly flouting the policy of the regional office. The problem of how to approach the countries was resolved when the regional office agreed that a medical officer from Headquarters, Dr Stephen Falkland, accompanied by Ladnyi, could visit a number of African countries early in 1967 so that the Director-General could report to the World Health Assembly in May of that year on each country's smallpox status and intended activities, if any, in accordance with the Assembly's request of 1966. Dr Falkland was specifically directed that under no circumstances should he propose to any country that it should undertake a programme. In the event of a display of interest, however, he carried with him a draft letter requesting assistance, prepared for the signature of the minister of health, as well as a draft plan of operations which could be readily adapted to the specific conditions of each country. He made brief visits to Burundi, Kenya, Rwanda, Tanzania and Uganda, all of which expressed interest in initiating smallpox eradication programmes and which forthwith sent formal requests to WHO for assistance.

Of the 5 countries dealt with in the present chapter, only Tanzania viewed smallpox as an important problem. However, to undertake eradication programmes, it was unnecessary for the governments concerned to commit substantial national resources. For each programme WHO agreed to provide an adviser, vehicles (including in some instances, motor cycles and bicycles), refrigerators, camping equipment, vaccine and bifurcated needles, as well as a sum of money to cover the costs of petrol and vehicle maintenance. The country's obligation was primarily to provide a small cadre of national staff. To offset the

Table 19.4. WHO support for the programmes in eastern Africa, 1967–1974 (US$)[a]

Year	Kenya	Uganda	Tanzania	Rwanda	Burundi	Total
1967	1 914	0	85 592	0	0	87 506
1968	51 934	0	110 781	33 180	52 912	248 807
1969	41 279	79 482	86 900	23 784	61 733	293 178
1970	52 006	20 216	80 663	24 417	46 306	223 608
1971	60 473	18 031	72 393	52 456	54 874	258 227
1972	30 514	18 374	75 168	32 711	29 941	186 708
1973	14 919	0	89 980	20 999	15 217	141 115
1974	11 690	0	0	0	0	11 690
Total	264 729	136 103	601 477	187 547	260 983	1 450 839
Per head of population	0.023	0.014	0.045	0.050	0.073	-

[a] Excluding the cost of vaccine.

additional expenditures necessary for salaries of these workers, WHO made available vaccine and transport, which hitherto had been at the charge of the government. In all, the Organization provided US$1 450 839 in support of programmes in eastern Africa, a sum equivalent to US$0.01–0.07 per head of population (Table 19.4). The individual governments disbursed no more—and in most cases less—to eradicate smallpox than they had spent on controlling the disease.

PROVISION OF FREEZE-DRIED VACCINE

The acquisition of adequate supplies of freeze-dried vaccine and their distribution presented a problem to WHO throughout most of the global eradication programme (see Chapter 11). In the countries of eastern Africa, as well as many of those in central and southern Africa, there were unique difficulties which required special solutions.

Attempts were made in all endemic areas to promote the local production of vaccine, but it was not practicable for every country to do so because of the considerable cost and effort needed to establish and maintain a laboratory. For some 50 years, the Kenyan Medical Research Laboratory had been producing liquid vaccine, which it sold to Tanzania and Uganda. Thus, it seemed logical to supply this laboratory with equipment and consultant assistance so that it might serve as a regional resource for the production of freeze-dried vaccine. UNICEF provided US$20 000 for the necessary equipment and in January 1967 WHO made available the services of a consultant. By April 1967, the laboratory, directed by Dr Geoffrey Timms, had succeeded in producing 4 experimental batches of freeze-dried vaccine and by October 1968 was producing sufficient vaccine of a consistently high quality to meet all Kenya's needs. As production increased, it became possible to supply neighbouring countries, but herein lay a quandary. Kenya needed to charge for the vaccine to recover production expenses. WHO's stock of vaccine, however, was being provided through voluntary contributions and then distributed free of charge to all endemic countries to encourage its use. Unless this had been done, many governments, lacking reserves of convertible currency, would have continued to use locally produced liquid vaccine. The purchase of vaccine from Kenya by WHO was not feasible, because several producers in Europe were anxious to sell vaccine and such a move might have endangered the donation programme (see Chapter 11); thus, WHO had adopted the policy of purchasing no vaccine whatsoever. The problem was ultimately solved by supplying Kenya with almost all the materials needed for vaccine production, thus enabling it to produce additional vaccine which could be donated to WHO for use in other African countries. In all, WHO provided some 31 million doses of vaccine for use in the countries of eastern Africa (Table 19.5), of which 15 million doses were produced in Kenya.

The distribution of vaccine in a timely manner to the numerous African countries was a factor that had to be taken into account. Vaccine was in short supply throughout most of the eradication programme, and it was therefore not possible to stockpile large reserves in the endemic countries. With the uncertain schedule of vaccination campaigns, the shipment of vaccine had to be planned in advance. Vaccine donated to WHO during the early years came primarily from Europe or North America and was maintained in a cold-storage warehouse in Geneva. With the extensive air transport network centred in Geneva, it was not difficult to deliver vaccine anywhere in the world at 48 hours' notice. Vaccine donated by Kenya, however, was shipped direct to neighbouring countries to minimize transport costs. Distribution systems were thus in place for national programmes to be sustained without large stockpiles.

A problem which had to be tackled was that of communication through the official channels of WHO. For an African country to obtain vaccine, the standard procedure called for a request to be directed to the WHO

Table 19.5. Eastern Africa: freeze-dried vaccine supplied through WHO, from 1967 onwards (thousands of doses)

Year	Uganda	Tanzania	Rwanda	Burundi
1967	0	1 014	0	1 000
1968	800	0	0	200
1969	1 100	2 500	1 050	0
1970	2 850	2 000	500	725
1971	1 000	1 990	0	758
1972	495	968	113	315
1973	500	820	205	0
1974	510	1 984	280	250
After 1974	1 260	4 153	1 148	241

Regional Office for Africa in Brazzaville, which would forward it to Geneva. Communication between African countries, however, was often much slower than communication between Africa and Europe, and inevitably there were delays in processing the request within the regional office. A telegraphic request through official channels sometimes took 4–8 weeks before being received in Geneva. Meanwhile, field programmes came to a halt. The difficulty was resolved simply by sending 2 telegraphic messages—an official one to the regional office in Brazzaville and an unofficial one to Geneva, on which action was promptly taken.

Freeze-dried vaccine which had been contributed to WHO was made available to several of the countries for use in their health services even before their formal mass vaccination campaigns began (Table 19.5). This vaccine was first used by Burundi and Tanzania at the end of 1967 and by Uganda early in 1968. Kenya began using locally produced freeze-dried vaccine in October 1968. Tanzania reverted briefly to the distribution of liquid vaccine during November 1968, when it received a bilateral donation of 300000 doses, but fortunately no further contributions of this type were received. Rwanda continued to use its own locally produced freeze-dried vaccine until early 1969, when the government was persuaded to stop production and to destroy all existing stocks.

THE VACCINATION CAMPAIGNS

Except for a pilot programme in Tanzania in 1968, during which 350 000 persons were vaccinated, none of the vaccination campaigns began until 1969. Meanwhile, the number of reported cases of smallpox in Kenya, Tanzania and Uganda fell sharply (see Table 19.1), from 3800 in 1966 to 2147 in 1967 and to only 597 in 1968. Rwanda, during this period, did not officially recognize cases of smallpox; and little can be said about trends in Burundi, whose reporting system was less adequate than the others. During these years, little had been done to change the reporting systems and there was no organized surveillance–containment activity. However, the trend in incidence was steadily downward and systems which had detected many cases in prior years were now reporting very few. The mass campaigns in Uganda, Burundi, parts of Tanzania, and in Nyanza Province, Kenya, in 1965–1966 were undoubtedly responsible in part for the decrease in the number of reported cases. Perhaps of greater importance was the provision of freeze-dried vaccine for use by the health services in the control of outbreaks and in the limited routine vaccination programmes in which some health centres were engaged.

However, as we shall see, the vaccination campaigns in Kenya and Uganda began *after* transmission had apparently been interrupted; in Tanzania, only 88 additional cases

Table 19.6. Eastern Africa: number of reported cases of smallpox, by month, 1969–1970

Country	1969											
	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Rwanda	0	0	0	0[a]	0	6	47	28	15	5	4	2
Burundi	1	4	0	0	0[a]	20	40	10	10	8	5	10
Tanzania	12	14	5	12	11	7[a]	13	4	5	21	9	4
Kenya	5	3	5	0	0	0	1	0	0	0[a]	0	0
Uganda	2[b]	1[b]	0	0	1[b]	0	0	0	2[b]	1[b]	2[b]	0

Country	1970											
	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Rwanda	43	186	3	5	0	0	0	3[b]	5[b]	8[b]	0	0
Burundi	0	0	3	95	1	7	20	60	5	6	0	0
Tanzania	1	1	1	23[b]	0	0	1	3	2	0	0	0
Kenya	0	0	0	0	0	0	0	0	0	0	0	0
Uganda	0	1[b]	0[a]	1[b]	0	0	0	0	0	0	0	0

NOTE: Cases are shown by month of detection; many of the patients concerned experienced the onset of illness one to several months earlier.

[a] Denotes beginning of mass vaccination programme.

[b] Cases resulting from importations.

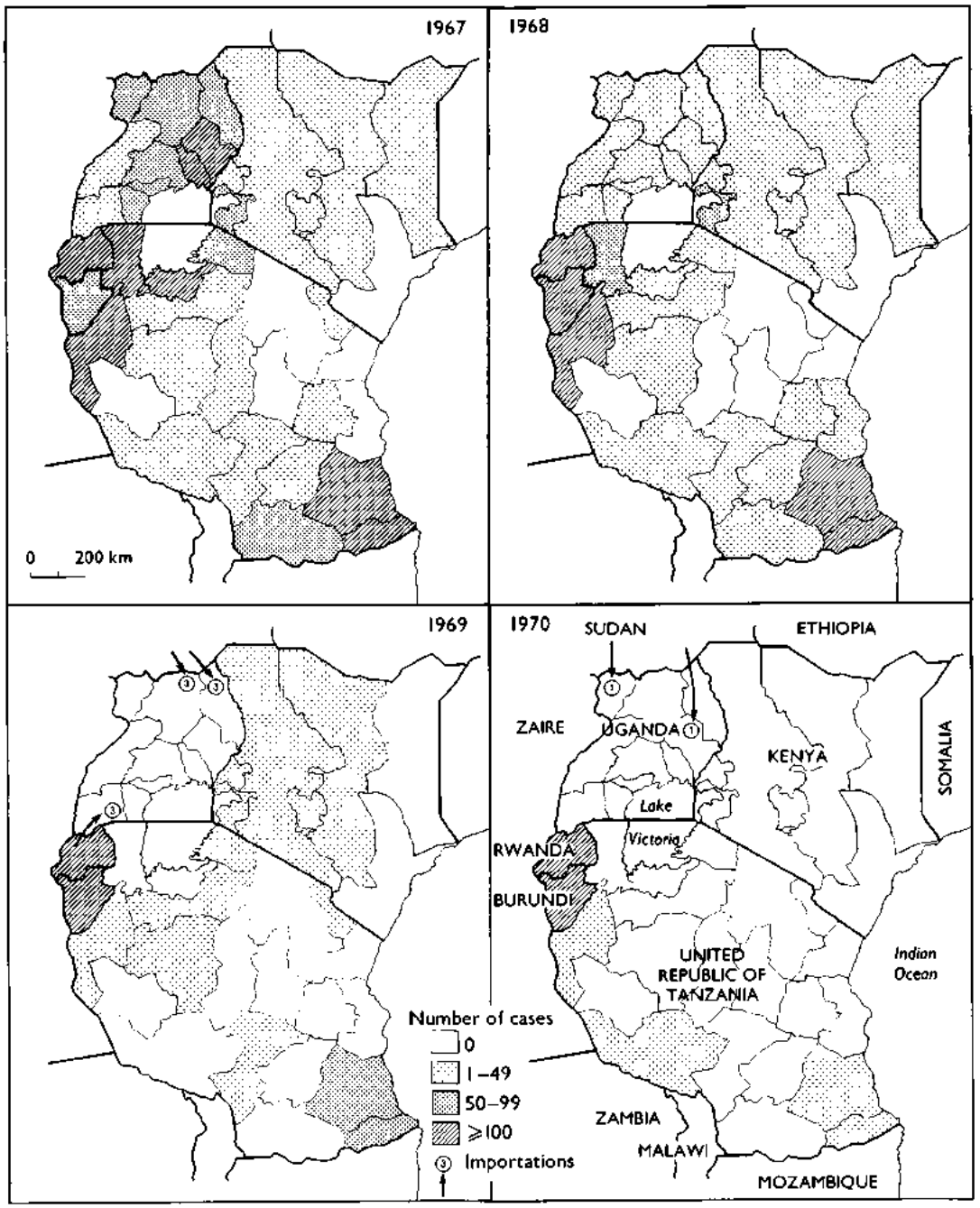


Fig. 19.2. Eastern Africa: number of reported cases of smallpox by administrative area, 1967–1970. The numbers of cases in Rwanda in 1967 and 1968 are estimated.

occurred after the beginning of the campaign, of which 23 are known to have resulted from an importation from Zaire (Table 19.6). The endemic spread of smallpox stopped only 13 months after the programme had begun in Rwanda and after 17 months in the case of Burundi.

The most heavily infected regions in 1967–1968 lay on the shores and in the vicinity of Lake Victoria (Fig. 19.2) and in the south-eastern area of Tanzania near the border with Mozambique. The region around Lake Victoria was also one of the most densely populated. As programmes began in 1969, Kenya

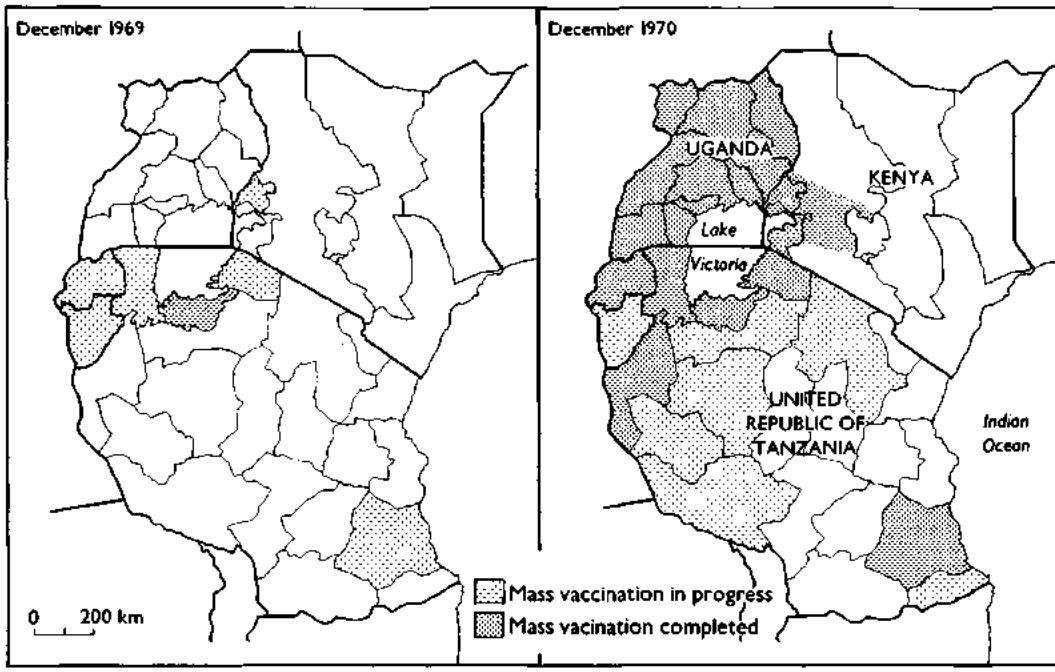


Fig. 19.3. Eastern Africa: status of vaccination campaigns, by administrative area, December 1969 and December 1970.

and Tanzania concentrated their efforts specifically in these areas (Fig. 19.3).

Kenya

A WHO technical officer from Belize, Mr Henry Smith, was recruited to assist in the development of the Kenya programme. He arrived in September 1968 and continued with the programme until February 1974. From October 1968 to the end of May 1969, Mr Smith visited all provincial and district headquarters, beginning with those in the west, whence cases were being reported, to demonstrate the use of the new bifurcated needle and the freeze-dried vaccine. At the time of his visit, stocks of liquid vaccine were replaced with freeze-dried vaccine. Staff in the districts were then given responsibility for training those in peripheral units. In Kenya at that time there were 163 health centres and 350 dispensary clinics; their staff reported having vaccinated 1.5 million persons in 1968 and 948 000 in 1969—about 25% of the population in all.

The beginning of the mass vaccination campaign had to await the delivery of vehicles, which usually arrived 12–18 months after they were ordered. The vehicles were delivered in the spring of 1969 and the programme began in October in Western Province, one of two small but densely populated south-western provinces inhabited by 40% (4.5 million) of Kenya's population. Kenya's last known case of endemic smallpox

Plate 19.2. Henry C. Smith (b. 1935) served as a WHO technical officer for smallpox eradication in Kenya, 1968–1974, before joining the programme in India.

occurred 4 months before the programme began.

Initially, the staff consisted of 2 supervisors assigned from the health services and 18 Kenyan National Youth Service Volunteers, who had completed elementary school and had undergone a 1-month training course. The team progressed from district to district. Three weeks before it was to begin work, Mr Smith, or sometimes the national programme director, met the district medical officer and health inspector to plan the campaign. Within the district, vaccinations were given to the inhabitants of one sublocation after another—a sublocation being a unit ranging in population size from a few hundred to 4000 and administered by a subchief. An assistant health inspector who worked in the area contacted each subchief to explain the purpose of the programme and to select a place of assembly for each sector at which approximately 300 persons would be expected to forgather. In the interests of economy of operation, the entire team worked in only one sublocation or a few adjacent sublocations each day. Assembly points included hospitals, health centres, dispensaries, schools, markets, chiefs' houses, shops, bus stops and wellheads. A few days before vaccinations were to be carried out, the subchief informed people of the schedule and the location of assembly points. Teachers were asked to pass on the details to parents and pupils. On the appointed day, 2 vaccinators (or more, if attendance was expected to be sizeable) were dispatched to the selected locations by Land Rover. One performed vaccinations while the other kept a simple tally by age group of the vaccinees. The vaccination centres were kept open throughout the entire day in order to give people sufficient time to attend, some being obliged to walk as far as 5 kilometres.

Because of the small number of staff, the vaccination campaign progressed so slowly that, by the spring of 1970, it was estimated that 10 years would be required to complete it. Accordingly, it was agreed that more National Youth Service Volunteers should be recruited and more supervisors assigned. By the end of 1970, the staff complement had grown to 50 vaccinators, 18 drivers and 8 health inspectors. In addition, it was agreed that when a team was in an area, local health staff who could be spared would work with it. The resources provided to the programme are shown in Table 19.7. With the increased complement of personnel, it was eventually possible to work in 10 districts simultaneously.

In May 1970, it was decided to administer BCG vaccine concurrently with smallpox vaccine to children under 15 years of age, and from then on the vaccinators worked as 2-man units. One vaccinator administered smallpox vaccine in one arm, using the bifurcated needle, and one administered BCG vaccine in the other arm, using a needle and syringe, and tabulated the numbers vaccinated. With this staff, between 400 000 and 500 000 smallpox vaccinations were performed monthly. By the end of 1970, the vaccination schedule had been completed in Nyanza and Western Provinces as well as in portions of the neighbouring Rift Valley Province (see Fig. 19.3). In other parts of Kenya the population was vaccinated during 1971 and, finally, the coverage was extended to the numerous inhabitants of Nairobi and its surroundings in 1972. In all, 10.5 million vaccinations were performed by the mobile teams and 5.6 million by the established health units during this period.

The only departure from the routine occurred in March and April 1971, when 2 outbreaks, one of 45 cases and one of a single case, occurred in the north-eastern part of Kenya as a result of importations from Ethiopia (see Fig. 19.4). The mass vaccination

Table 19.7 Eastern Africa: principal components of support to the programmes (exclusive of vaccine)

	Kenya	Uganda	Tanzania	Rwanda	Burundi
Provided by WHO:					
Advisers	1	0	2	1	1
Vehicles	35	26	51	9	13
Motor cycles			10	4	
Bicycles	141	141	108		
Refrigerators	13	20	82	32	12
Annual petrol/vehicle maintenance costs (US$)	6 000	10 000	20 000	15 000	15 000
Provided by government:					
Number of personnel (maximum)	76	700[a]	72	27	50

[a] During one period of 6 months.

campaign in this area had been scheduled to begin in April and last throughout June 1971, but its date of commencement was advanced to March. Subsequently, 6 vaccination/case-search rounds were conducted in this and 5 other northern districts that bordered on Ethiopia and the Sudan and were considered to be at high risk.

Except for Rwanda, none of the 5 countries followed the programme for assessment recommended in the WHO *Handbook for Smallpox Eradication Programmes in Endemic Areas* (SE/67.5 Rev.1). The handbook called for an assessment team to visit a 10% random sample of villages 1–2 weeks after vaccination to determine coverage and the proportion of people successfully vaccinated. As was the case in a number of countries, health officials resisted the diversion of personnel and vehicles from the vaccination campaign itself. To determine coverage in Kenya, the number vaccinated was simply compared with the estimated population in the area—an unsatisfactory procedure in a country where census data were so imprecise. Approximately 100 children were examined one week after vaccination to determine whether a sufficient proportion had been successfully vaccinated. Definitive information about the degree of success of the vaccination campaign did not become available until the conclusion of the programme, when, in 1972, 2 WHO staff from the WHO Epidemiological Surveillance Centre in Nairobi undertook a carefully designed cluster sample survey. Approximately 2000 persons were examined in each of 5 different provinces. The results are shown in Table 19.8.

The vaccination coverage of individuals aged 5 years and over was satisfactory in the Central, Eastern and Coast Provinces but not in Western and Nyanza Provinces, in which the programme had first been launched and had been completed in 1970. In these latter two provinces, the vaccination coverage of children under 5 years of age was substantially below expected levels; this was partly accounted for by the fact that health centres were vaccinating only about 25–30% of those born subsequent to the 1970 campaign.

At the conclusion of the campaign, in July 1972, 22 sectors were identified, to each of which a team with a vehicle was assigned. The teams were to proceed from one sublocation to the next, vaccinating those eligible for vaccination and inquiring at schools, markets and health units about possible cases that might have occurred during the preceding 3 months. Each team was expected to complete a tour of its sector once a year; in high-risk areas, the schedule was intensified to once every 3–6 months. The teams were called surveillance teams, but in fact their principal responsibility was to provide maintenance vaccination. The system remained in operation for little more than a year.

Uganda

Like Kenya, Uganda had a reasonably extensive network of health centres and clinics and a complex of roads reputed to be the best in eastern Africa. A mass vaccination campaign using liquid vaccine was completed in 1966, following which the number of cases of smallpox diminished to only 365 in 1967 and 55 in 1968. Between 600 000 and 900 000 persons were being vaccinated annually in the various health establishments, and in 1969 freeze-dried vaccine supplied by WHO was introduced for use throughout the country. Because liquid vaccine had been employed in the previous vaccination campaign and because it was known that many of the vaccinations had not been successful, Uganda agreed in mid-1968 to undertake a special 3-year national vaccination campaign. WHO provided the necessary vehicles and equipment. However, the government later decided to abandon this schedule in order to conduct, in 1970, a national mass vaccination cam-

Table 19.8. Kenya: results of vaccination scar surveys in 5 provinces, by age group, 1972

Age group (years)	Western		Nyanza		Central		Eastern		Coast	
	Number examined	% with scar	Number examined	% with scar	Number examined	% with scar	Number examined	% with scar	Number examined	% with scar
0–4	472	51.7	444	45.9	493	76.5	486	76.1	471	62.0
5–14	645	77.8	628	74.7	774	89.2	719	90.8	570	90.0
⩽15	902	81.3	943	72.1	827	86.7	866	83.8	1 066	89.3
Total	2 019	73.2	2 015	67.8	2 094	85.2	2 071	84.4	2 107	83.3

paign to be completed in just 6 months. To help to prepare the work, Dr Georgij Nikolaevskij, of the WHO Headquarters Smallpox Eradication unit, was detailed to Uganda for a 5-month period. He assisted Dr Yurij Rikushin, a WHO medical officer originally assigned to Uganda for BCG vaccination. District health inspectors in each district organized the programme, which required the population to assemble for vaccination at collecting points. Vaccination staff were divided into groups of 3 or 4 persons who moved from subcounty to subcounty. In all, some 700 public health staff were engaged in the campaign. Between March and August 1970, 8.5 million vaccinations were performed in a population then estimated to be 9.8 million. There was no special assessment of the campaign to measure the prevalence of vaccination scars after it had been completed, but most believed that it had been generally well executed. Like the programme in Kenya, however, it was begun many months after smallpox transmission had been interrupted.

Following the campaign, vaccination continued to be performed by the various health centres in the country but only 100 000–200 000 persons were vaccinated annually, a figure equivalent to perhaps half the number of children born each year. In addition, sporadic campaigns which involved the vaccination of about 100 000 persons were conducted in areas bordering on the Sudan following the importation of cases from that country.

Such knowledge as was available regarding the level of vaccinial immunity at the time was provided by 2 surveys carried out in different parts of northern Uganda (Table 19.9).

Both surveys were conducted in areas convenient of access by road, immediately after special area-wide mass campaigns had taken place. One must assume that vaccinial immunity in more remote areas of these districts and in other parts of Uganda was substantially below the levels shown in Table 19.9.

I.D. LADNYI, c. 1969

Plate 19.3. Yurij P. Rikushin (b. 1923), a WHO medical officer working in tuberculosis control in Uganda, 1965–1971, also acted as the smallpox eradication adviser there and was instrumental in organizing Uganda's 6-month intensive mass vaccination campaign.

Tanzania

Of the 5 countries, Tanzania was the only one which had expressed genuine enthusiasm about undertaking a programme. A thousand or more cases of smallpox had been reported almost every year since the 1950s, and in many outbreaks case-fatality rates of 5–10% had been recorded. Vaccination with liquid vaccine had been provided in health centres throughout the country, but no special programme had been conducted until 1965–1966, when the number of reported cases increased to 2762 in 1965 and to 3027 in 1966. During these 2 years, a mass campaign was conducted in which 6 million vaccinations were given and, subsequently, some 2–2.5 million vaccinations, with the low-potency liquid vaccine, were perfotmed annually in health units, which then consisted of 105 hospitals, 54 rural health centres and 1442 dispensaries. However, 1629 cases were reported in 1967—and reporting in Tanzania was considered to be less complete than in Kenya or Uganda.

In August 1967, WHO and the government agreed on a plan of operations which provided for transport, equipment and sup-

Table 19.9. Northern Uganda: results of vaccination scar surveys, by age group, 1972

Age group (years)	February 1972		April 1972	
	Number examined	% with scar	Number examined	% with scar
<1	120	17.5	109	51.4
1–4	449	82.6	205	86.8
5–14	491	90.8	331	90.3
⩾15	508	95.0	1 226	97.3

plies of freeze-dried vaccine, as well as the assignment of a WHO medical officer, Dr Roger Lyonnet, and a technical officer, Mr D. G. Michalatos. The WHO staff arrived in the late spring of 1968, and in July 1968 a pilot project was begun in Geita District (population, 385 000) in northern Tanzania. This district had reported the highest incidence of smallpox of any in the country in 1966–1967 and was considered to be one of the most difficult in which to work because of poor roads and extensive swamps. During a 5-month period, a team of 24 vaccinators, a supervisor and 4 drivers performed vaccinations equal in number to more than 90% of the population.

Lack of government funds then resulted in the suspension of the campaign for 7 months, until July 1969, when it was resumed in the endemic north-western districts (see Fig. 19.2) and at the end of the year in 2 endemic south-eastern districts. Three mobile teams, each consisting of 23 persons, conducted the campaign under the direction of each area's district health inspector. The teams were subdivided into 4 units, each comprising a supervisor and 4 or 5 vaccinators and equipped with a motor vehicle, 2 bicycles and a kerosene-operated refrigerator. Political leaders, called "ten-cell chairmen," played an important role. Each was contacted one or two weeks before the team was due to arrive and was asked to prepare a list of all residents in the area for which he was responsible. When the team arrived, the residents were assembled and each was summoned by name for vaccination. The system might appear cumbersome and time-consuming, but in fact the vaccinators consistently averaged more than 500 vaccinations a day. They continued to achieve this norm even when, in 1970, they undertook the additional task of administering BCG vaccine to children under 15 years of age. The system was an unusual one but it worked well in Tanzania, in which the political structure was highly organized. An independent cluster sample survey conducted in Geita District by a team from the WHO Epidemiological Surveillance Centre in Nairobi revealed that 94% of the persons examined had vaccination scars at the conclusion of the programme (Table 19.10).

Later surveys, conducted during 1970 at the conclusion of campaigns in 6 regions, revealed comparable results (Table 19.11).

Although by the end of 1969 the vaccination campaign had been completed in only 1 district and had just begun in 3 others, the number of reported cases of smallpox that year decreased to 117. Reporting was still inadequate, since little had been done to improve the national reporting system; however, this was the lowest total of cases ever recorded. Even if the reporting system had not improved, it certainly did not appear to have deteriorated. Finally, in 1970, the investigation of some cases began. Of 3 outbreaks examined, 1 (in April) had resulted from an importation from neighbouring Zaire. Cases were reported from only 4 regions (Fig. 19.2), and in September the last case was found.

The programme continued, region by region and district by district, at length concluding with the vaccination of the population of the then capital, Dar es Salaam, in August 1973. While in most countries the residents of the capital city were the first to be vaccinated, they were left until last in Tanzania, since Dar es Salaam, situated on the coast, was far away from the known endemic areas. In all, 19.8 million persons were vaccinated against smallpox between 1967 and 1973 and 3.7 million under 15 years of age received BCG vaccine. After September 1970, vaccinators during their visits reported 23

Table 19.10. Tanzania, Geita District: results of vaccination scar survey, by age group, 1969

Age group (years)	Number examined	With scar	
		Number	%
0–4	210	197	93.8
5–14	293	283	96.6
⩾15	654	608	93.0
Total	1 157	1 088	94.0

Table 19.11. Tanzania: results of vaccination scar surveys in 6 regions, by age group, 1970

Region	0–4 years		All ages	
	Number examined	% with scar	Number examined	% with scar
Mara	3 251	98.9	9 423	93.1
West Lake	4 341	96.0	14 608	95.4
Mtwara	8 116	98.1	35 482	98.2
Shinyanga	709	97.5	1 544	98.2
Tabora	897	91.8	3 704	97.2
Kigoma	342	93.0	897	94.9

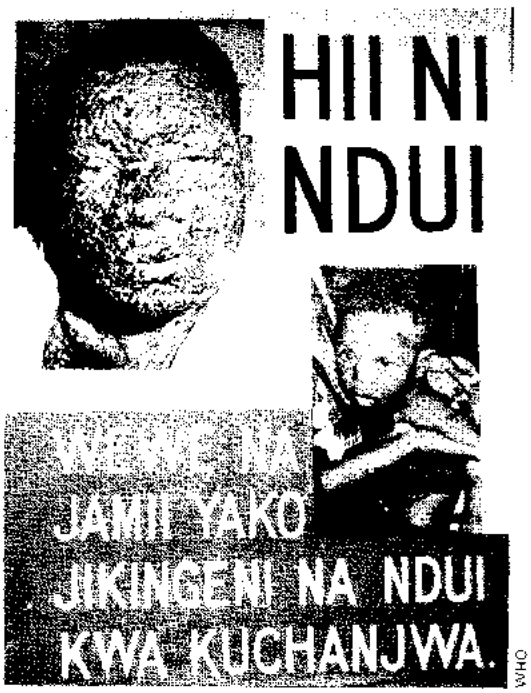


Plate 19.4. Tanzanian posters in Swahili were widely distributed in 1969, reading: "This is smallpox. You and your family protect yourselves by getting vaccinated".

suspected cases but none proved to be smallpox.

On completion of the programme, mobile teams continued to vaccinate and to search for cases in remote and border areas; the health services vaccinated about a million persons each year thereafter but, as in Kenya and Uganda, interest in the programme diminished sharply.

Rwanda and Burundi

The programmes in these densely populated countries, each with some 3.5 million inhabitants, were a study in contrasts. In both, the responsibility for operating the programme was largely delegated to their respective WHO smallpox advisers. One of these, Dr Celal Algan, was an energetic worker, well acquainted with conditions in the field, who, with the help of Rwandese staff, conducted one of the most effective programmes in Africa. The other, who was assigned to Burundi, rarely travelled to the field and had little apparent capacity for organization; the programme in Burundi reflected these shortcomings.

In both countries, the population lived in small hamlets and hillside villages scattered over a tropical and subtropical upland plateau. Roads were few and often impassable during the February–May rainy season. Hospitals, health centres and dispensaries, some operated by the government and some by missionaries or other private voluntary organizations, were comparatively numerous. In 1971 there were 157 hospitals, health centres and dispensaries in Rwanda and 104 hospitals and dispensaries in Burundi. Vaccination was offered at all these health units; about 10–15% of the population were vaccinated each year. The vaccine used was a liquid product which had been manufactured by a laboratory in Butare (Rwanda) since 1953. Beginning in 1965, this laboratory also produced some freeze-dried vaccine which, as has been mentioned earlier, was prepared in 600-dose vials. These vials contained such a large quantity of vaccine that it was often kept, unrefrigerated, for many days or even weeks, with a consequent loss of potency after the first day.

Rwanda

Vaccination in Rwanda had been performed primarily by 2 teams, each consisting of 3 persons, who shared a vehicle and travelled regularly to 400 vaccination points established at health facilities and schools. A sample scar survey conducted in 1968 of 10 404 persons in 3 different prefectures showed a generally low level of vaccinial immunity, especially among children (Table 19.12).

An agreement was signed with WHO in April 1968 which provided for the assignment of a WHO medical officer and the supply of vehicles and equipment, vaccine and needles, as well as for the costs of petrol and vehicle maintenance to be met by WHO. However, at the end of 1968, the Ministry of

Table 19.12. Rwanda: results of vaccination scar surveys in 3 prefectures, by age group, 1968

Age group (years)	Number examined	% with scar		
		Kibungo	Kigali	Gisenyi
0–4	1 920	0	3	25
5–14	3 482	44	21	79
≥ 15	5 002	72	69	85
Total	10 404	48	43	73

Health and WHO staff working in the country re-evaluated the plan and decided to combine the field activities with those of a BCG vaccination campaign then under way. Dr Algan, at that time the WHO adviser for tuberculosis control in the country, volunteered to assume responsibility for both activities.

In mid-April 1969, the programme began operations with a supervisor and 10 vaccinators who worked in pairs, one administering BCG vaccine and the other smallpox vaccine. Only a single vehicle was available, and so the team moved as a group to the various administrative units (prefectures), where vaccination was performed at collecting points. Areas from which cases were reported were attended to first. Hospitals and health clinics were supplied with vaccine and encouraged to participate in giving vaccinations.

As was the practice in other countries, Dr Algan and his Rwandan counterpart held meetings with local authorities beforehand to

Plate 19.5. **A:** Celal Algan (b. 1926), previously the WHO medical officer assigned to Rwanda for tuberculosis control, assumed responsibility in 1968 for organizing the smallpox eradication work in a campaign combining the administration of smallpox and BCG vaccines. The well-planned, rigorously supervised operation completed its 36-month work plan in half that time, while simultaneously developing an effective surveillance programme. Subsequently, as the WHO regional adviser on smallpox eradication in Africa (1975–1980), Algan organized the extensive activities required for the certification of eradication. **B:** Land Rovers move out for field work towing trailers with camping equipment. **C:** Rwandan vaccination team

explain the programme and to identify the most suitable collecting points and work out the best schedule. Local political leaders were given the responsibility for convening the people on the appropriate day and, later, for the reporting of smallpox cases. Concurrent assessment of the campaign was by random sample evaluation to ascertain take rates.

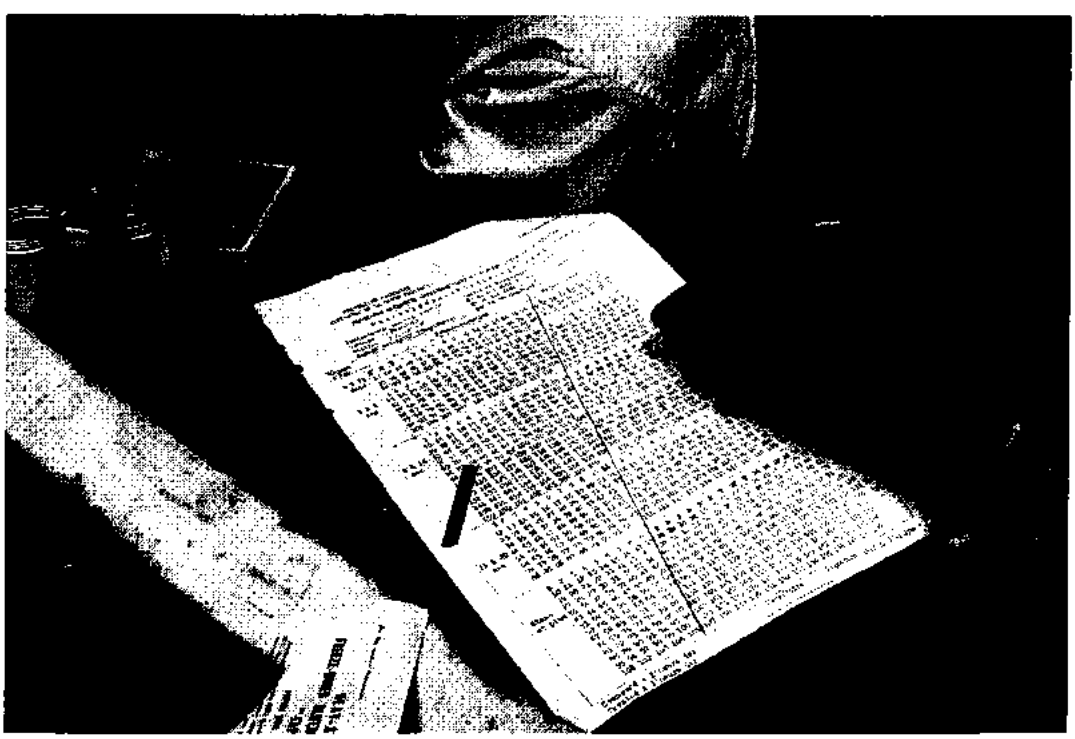
From the beginning, the team worked conscientiously and well, initially averaging 750 vaccinations per vaccinator per day and later as many as 1500 vaccinations per vaccinator per day. The productivity reported was in fact so high that the figures were viewed with scepticism by Ladnyi and WHO Headquarters staff. Ladnyi, however, confirmed the validity of the data during a special visit, noting in passing that the vaccinators complained only of sore fingers and wondered whether thimbles could be provided.

In October 1969, the vehicles intended for the programme were delivered and, with additional transport available, the complement of staff was increased to 27 (2 supervisors and 25 vaccinators, 5 of whom served as drivers); the personnel were divided into 3 teams, of which 2 were occupied with vaccination and the third, headed by Dr Algan, with surveillance–containment. By the end of 1969, 989000 persons had been vaccinated against smallpox by the mobile teams and 54 000 children had been given BCG vaccine.

During 1970, the investigation of 18 reported cases led to the discovery of 235 additional cases. After April, only 3 outbreaks, consisting of 3, 5 and 8 cases respectively, were discovered; each had resulted from importations from Zaire.

By the end of October 1970, only 18 months after the vaccination campaign began, the programme had been completed. During this period, the teams had vaccinated more than 3 million persons. A scar survey conducted in 1971 showed that, of those examined, 87% of children aged 0–4 years had vaccination scars, as did 97% of those aged 5–14 years and 93% of persons aged 15 years and over.

After the programme had been completed, hospitals and clinics continued to administer smallpox and BCG vaccines, while 8 teams, each consisting of 3 vaccinators, travelled throughout the more remote areas, especially those bordering Zaire, to search for cases and to vaccinate.



C. ALGAN

Plate 19.6. The recording form used in vaccination centres in Rwanda. The numbers of smallpox vaccinations and revaccinations administered could be quickly and easily noted by age group.

Table 19.13. Burundi: results of vaccination scar surveys in 3 prefectures, by age group, June 1968

Age group (years)	Kitega		Ruyigi		Bururi	
	Number examined	% with scar	Number examined	% with scar	Number examined	% with scar
0–4	174	7	94	87	125	96
5–15	539	78	487	95	144	98
⩾16	276	73	347	93	67	82

Burundi

Vaccination in Burundi had traditionally been performed by health units. In 1966, however, 500 000 persons were vaccinated during a special mass vaccination campaign undertaken after the occurrence of 1213 reported cases of what was said to have been variola minor. Sample surveys carried out by Ladnyi in 3 prefectures of Burundi in June 1968 revealed a remarkably high level of vaccinial immunity in all age groups in 2 of the areas in which the campaign had been conducted, and satisfactory levels in individuals aged 5 years and over in the third area (Table 19.13).

A plan of operations for an eradication programme was agreed on and signed in December 1967 by WHO and the government. How much smallpox might be present was unknown, since reporting was very incomplete. Only 74 cases were recorded in 1967, but the number rose to 301 in 1968.

In December 1968, a WHO medical officer arrived on assignment, along with supplies and equipment. Field activities began in May 1969 with 2 (later 4) mobile vaccination teams, each consisting of a supervisor, 4 vaccinators, an enumerator and a driver. The number of staff increased to 31 by mid-1969 and to 50 by 1971. The method of work was similar to that in Rwanda although never characterized by the same degree of careful planning and diligence. During 1969, only 415 705 vaccinations were performed, a number far lower than in Rwanda. Ladnyi, who visited the programme in February 1970, discovered that none of the vaccine was being kept under refrigeration, that vaccinators were issuing each vaccinee with a signed and officially stamped certificate of vaccination and that vehicle maintenance was virtually nil. The existing stocks of vaccine were destroyed and new supplies were flown in; the time-consuming practice of issuing individual certificates of vaccination was stopped; but a proposal to replace the WHO smallpox adviser was rejected. Fortunately, a new WHO country representative, Dr Christos Karamustakis, arrived at this juncture. An intelligent, industrious person who had worked previously in Zaire and knew the smallpox programme there, he assumed on a part-time basis an overall supervisory role and, thereafter, the programme proceeded better. However, despite a far greater complement of personnel than in Rwanda, and despite the absence of the requirement for simultaneous administration of BCG vaccine, the mass vaccination campaign in Burundi took more than 2 years to complete and did not conclude until June 1971.

Table 19.14. Burundi: results of vaccination scar survey, by age group, 1973

Age group (years)	Number examined	% with scar
0–4	6 783	5.9
5–14	103 815	69.8
⩾15	90 118	70.0
Total	200 716	67.7

In all, 2 997 500 vaccinations were performed between 1969 and 1971. No concurrent assessment of coverage was performed, nor were vaccinations checked to find out whether they were successful. Following the campaign, vaccinial immunity was not high, as was revealed in a 1973 sample survey conducted by a team from the WHO Epidemiological Surveillance Centre in Nairobi (Table 19.14).

The local health services were expected to continue the vaccination campaign but little had been done to obtain their cooperation and thus the number of vaccinations performed in 1972 dropped to only 30 000. Other WHO staff were brought in to help to organize an effective reporting and maintenance vaccination programme, and by 1973 reporting had begun to improve and the number of vaccinations to increase.

SMALLPOX OCCURRENCE, 1969–1970

Only 355 cases were reported from the 5 countries in 1969 and 484 cases in 1970. How accurately this reflects the true incidence of

smallpox is difficult to assess. The eradication programmes consisted essentially of the traditional mass vaccination campaigns of the past, few of which incorporated either concurrent assessment of coverage or a special surveillance–containment element.

A national surveillance programme which served to ensure that all suspected cases were investigated and the outbreaks contained was a difficult concept for the countries to grasp and to implement. This was especially true of the former colonies of the United Kingdom, since their health services tended to be much more decentralized, the primary responsibility for health programmes being vested in district medical officers. This policy of decentralization of authority and responsibility offered many advantages in implementing a variety of programmes but not for the development of a national surveillance programme. District medical officers considered the control of smallpox to be specifically their own responsibility and resented the intrusion of a national presence. Where district medical officers were competent and diligent, this was not a problem; but many were not, and for all of them smallpox was but one of an array of problems and not always of high priority. A report of the occurrence of smallpox evoked the typical response that cases occurred in the province from time to time.

Ladnyi struggled to try to improve reporting and surveillance but, with responsibility for 19 countries, could devote little time to any single country. Moreover, he had been instructed by the regional office that he was not to undertake travel unless a visit was specifically approved in advance by the country and by the regional office, a process which he found to require at least 6 months. He ultimately decided to sidestep this restriction by sending a telex to the regional office informing it of his proposed travel plans and indicating that he would proceed unless instructed otherwise within the next 2–3 weeks. Rarely did the regional office reply in less than 4–8 weeks to any communication. A pattern therefore evolved in which Ladnyi proposed a trip and, receiving no reply, went ahead with his travel plans and eventually returned to Nairobi. After his return, he often received a telex advising him not to undertake the proposed trip.

In 1969, with so few cases being reported in eastern and southern Africa, it seemed that transmission would be interrupted quickly whatever the status of the vaccination campaigns. Accordingly, on 4 June 1969, Henderson wrote to the regional office and to Ladnyi in the following terms:

> "I believe that it is absolutely, vitally and unequivocally essential that provision be made for a responsible person, preferably a medical officer, to investigate personally each and every case to verify the diagnosis and to assist with or carry out himself the necessary investigations and containment activities. Any plan not incorporating this particular feature is doomed to failure . . . Experience throughout the world both in endemic and in non-endemic areas has clearly shown that when full responsibility is entrusted to the district health authorities, the results obtained are highly irregular and frequently unsatisfactory."

Interestingly, eastern Africa in particular was to disprove Henderson's sweeping prediction of failure. The status of smallpox in 1969 was anything but clear. Kenya ceased to detect cases that year. Burundi recorded 108 cases and Tanzania 117 cases, but in neither country was there an adequate surveillance programme. In Rwanda, on the other hand, efforts were made to improve reporting and to investigate outbreaks. There, Dr Algan sought to obtain reports from the health units and, when outbreaks were found, redirected the programme to conduct mass vaccination in the infected areas. Virtually all cases in Rwanda were those detected by the special teams. It is probable that reporting was also somewhat more complete in 1969 in Burundi and Tanzania because vaccination teams worked in infected areas and detected cases in the process. However, it is likewise probable that some of the reported cases were misdiagnosed cases of chickenpox. Uganda, for example, originally reported 19 cases in 1969, but when these were investigated by a WHO consultant, only 9 were found to have been smallpox.

In 1970, Kenya reported no cases and Uganda only 2; the latter, when investigated by a WHO consultant, were found to have been infected in the Sudan and Rwanda respectively. Tanzania detected only 32 cases, the last in September. Twenty-three of the cases occurred following an importation from Zaire; the others were not investigated. In Burundi vaccination teams found 197 cases, about which nothing more is known; the last of them occurred in October. Rwanda reported 253 cases in 1970, of which 18 were notified by the health services and the rest detected by the surveillance team. Transmis-

Table 19.15. Rwanda: number of cases of smallpox, by age group, 1969–1970

Age group (years)	Number	%[a]
<1	50	14.3
1–4	112	32.1
5–14	162	46.4
⩾15	25	7.2
Unknown	11	–
Total	360	100.0

[a] Percentage distribution calculated on total cases with known age (349).

sion in Rwanda was interrupted in April 1970, although 3 outbreaks resulting from importations from Zaire occurred between August and October. Data regarding the age distribution of cases throughout 1969–1970 are available only from Rwanda (Table 19.15). Virtually all the cases were in children under 15 years of age, almost half of them under 5 years old.

Increased confidence that reporting was reasonably complete in 1970 was provided by the expanding vaccination campaigns, which served both to improve vaccinial immunity and to detect any cases that were present. In October 1970, the last cases were reported from these 5 countries, but not until nearly a year later could it be stated with confidence that transmission had actually been interrupted.

The rapid disappearance of smallpox from this area was surprising considering the perfunctory surveillance and containment activities. Levels of vaccinial immunity varied widely from place to place but, except where the systematic vaccination campaigns had been conducted, they were not generally high. Indeed, smallpox had disappeared from all but the densely populated areas of Burundi, Rwanda and Tanzania before the campaigns began. In retrospect, a combination of factors was probably responsible: (1) a generally scattered population with few large urban centres; (2) limited travel by most of the population, many of whom respected the numerous tribal boundaries; (3) prevalent, although not universal, tribal traditions which called for patients to be isolated in a separate hut and cared for by someone who had had smallpox; (4) a comparatively extensive network of health centres which, when freeze-dried vaccine was made available, successfully immunized a large proportion of people; and (5) the presence of a form of smallpox which spread less readily than did variola major in Asia and against which successful vaccination provided a longer-term immunity.

After 1970, outbreaks were reported only in Kenya and Uganda, in the former following importations from Ethiopia and Somalia, and in the latter from the Sudan.

IMPORTATIONS INTO UGANDA

It is probable that transmission in Uganda was interrupted in 1968. Only 9 cases were detected in 1969, and although the sources of these outbreaks were not clearly traced, 6 occurred in Sudanese refugee camps in its northern districts and the other 3 in the south among refugees from Rwanda. In 1970, 1 case occurred in the north in a refugee infected in the Sudan and 1 case in a person infected in Rwanda. During 1971–1972, Uganda recorded 35 cases, all in its northern districts among Sudanese refugees and members of the local population who were in contact with them. These are shown as imported cases in Table 19.1.

Juba Province in the southern Sudan lay just across Uganda's northern border and there a protracted civil war had been in progress. Tens of thousands of Sudanese refugees had taken up residence in northern Uganda and many continued to move back and forth between the two countries. The health services in Juba had been devastated by the war, vaccinial immunity was low, and, throughout 1972, smallpox was widely prevalent.

In October 1970, when Uganda had completed its mass vaccination campaign, it reverted to its previous pattern of operations, whereby vaccination was performed at clinics and health centres; district health inspectors assumed responsibility for surveillance activities and the containment of any outbreaks that were found. WHO recommended that a national surveillance team should be constituted to improve reporting and to participate in the investigation of any reported outbreaks, but this advice was not followed.

In 1971, 19 cases were reported from the northern districts of Acholi and Madi, 15 of which occurred in Sudanese immigrants; 4 local residents were infected by them. In 1972, 16 further cases were detected in this same area, primarily among Sudanese nationals. WHO staff who visited the area discovered that containment measures were not

promptly taken, the investigation of outbreaks was perfunctory, containment was poorly executed and a number of cases reported locally were not notified to the national authorities. Fortunately, in this sparsely settled, reasonably well vaccinated area, the spread of smallpox was even less efficient than the performance of the staff.

In early 1973, a special training programme in surveillance–containment was conducted for the staff in northern Uganda, and in April a central surveillance team was constituted to investigate all suspected cases. A number of suspected cases were competently investigated and specimens obtained, but none proved to be smallpox. Meanwhile, Uganda's only remaining endemic neighbours, Zaire and the Sudan, succeeded in interrupting transmission—Zaire in June 1971 and the Sudan in December 1972. Thus, the surveillance team began work in Uganda after the risk of importations had all but ceased, ironically paralleling the execution of its national vaccination campaign, which began after smallpox transmission had been interrupted.

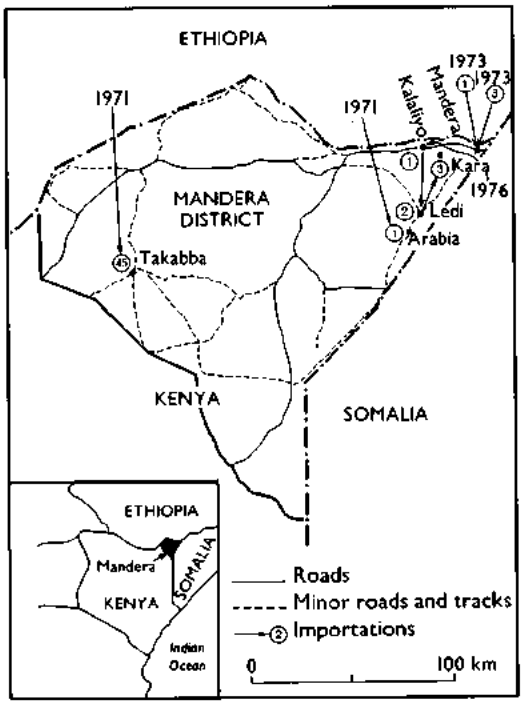


Fig. 19.4. Kenya: sources of importations of smallpox, 1971–1976.

IMPORTATIONS INTO KENYA

Kenya, in contrast to Uganda, initially took more vigorous steps to improve reporting and established a national surveillance team in 1970. Six suspected cases were investigated in that year, all of which proved to be chickenpox. In March 1971, a nomadic herdsman from Ethiopia, travelling while ill, crossed the border and infected residents in a village some 70 kilometres south of the border. Subsequently 44 more cases occurred in 3 generations of transmission, 5 of the cases being fatal. The large proportion of deaths was unusual for outbreaks in the Kenya–Ethiopia area at this time, but whether the outbreak was due to variola major rather than variola minor is unknown. Mass vaccination had not yet been conducted in this area but, because of the outbreak, teams were quickly transferred to the district. Six thousand persons were vaccinated in and around the village, and the teams subsequently searched and vaccinated the entire district. No further cases were discovered.

In April 1971, another case was reported from a village 150 kilometres east of the first (Fig. 19.4). The patient was an Ethiopian adult visitor who resided just 14 kilometres north of the border. More than 95% of the village people had already been vaccinated and no further cases occurred.

The national mass vaccination campaign concluded in June 1972 and, at that time, the country was divided into 22 sectors, each with a mobile surveillance team which was supposed to be responsible for surveillance and for the vaccination of nomadic and other groups considered likely to import smallpox. By then, Ethiopia was Kenya's only neighbour with endemic smallpox.

In Kenya the surveillance programme proved to be little better than in the other countries. In part, this can be ascribed to the fact that no surveillance teams had been established before transmission was interrupted, and thus they had no experience either in the investigation or in the containment of outbreaks. Moreover, the absence of cases understandably led to complacency. Sustaining interest in smallpox eradication after transmission had apparently been interrupted was difficult in all countries and especially difficult in Kenya. Following the outbreaks in March and April 1971, no further cases were detected for more than 2½ years.

On 30 December 1973, a 25-year-old man with smallpox was found in Mandera in north-east Kenya at the border with Ethiopia and Somalia. He had travelled 150 kilometres from an area in Ethiopia in which smallpox was known to be occurring. Containment vaccination was begun, and during the campaign a second case was discovered. The patient was a 23-year-old woman, who developed rash on 27 January and subsequently infected 2 other people. She had arrived in Mandera only 2 days before becoming ill and thus represented a second importation. The source was said to be a Kenyan village near the Ethiopian border, some 80 kilometres to the west. The fact that no investigation of this area was undertaken (although no further cases were reported) is indicative of the quality of the surveillance.

Again, 2 years were to elapse without cases. Meanwhile, Ethiopia reported its last cases in August 1976. In late September, however, Somalia reported its first cases for almost 2 years, in the capital, Mogadishu, supposedly resulting from importations from Ethiopia. As at the end of December, 39 cases had been reported, all in Mogadishu (see Chapter 22). When the report of cases in Somalia was received, a Kenyan team was sent to the border area to undertake an active search for cases. This team then represented virtually the only surveillance unit within 150 kilometres or more, since because of fighting in the area, Ethiopian teams had to remain at least that distance from the Kenyan border. Somali staff, if they were finding cases outside Mogadishu, were not reporting them.

That smallpox did not spread into Kenya must be attributed more to good fortune and to a sparse population than to the work of the inexperienced surveillance team. In December 1976, smallpox was again introduced into Mandera District (see Fig. 19.4). From the available, and somewhat conflicting, reports, it appears that a 40-year-old Kenyan man, who had been studying in an Islamic school near Mogadishu, became ill with smallpox on 26 December. He was then staying with his brother in a village, Kalaliyo, 29 kilometres west of Mandera town; 3 days later, he travelled some 35 kilometres south to a village, Ledi, to stay with his sister, and soon thereafter he returned to Somalia. The health officer in Mandera, informed that a case resembling smallpox had been seen in Ledi, sent a health inspector and a vaccinator. On arrival, they were told that the patient had left; they returned without vaccinating anyone. On 13 January 1977, a subchief reported that the patient's sister had developed a rash. This time, the surveillance team went to Ledi, obtained a specimen and departed. Eleven days later, a report was received from a Nairobi laboratory that the specimen contained smallpox virus. On 26 January, the team again went to Ledi and found that the family had departed for a village (Kara) some 50 kilometres to the north-east. Another day elapsed before they could be found. Vaccination was then begun but 2 daughters became ill with smallpox on 22 and 27 January and another daughter (still unvaccinated) on 7 February. The patients were advised to stay in the house, but it was learned later that the mother regularly left the house to obtain water from a nearby waterhole frequented by a number of people.

Additional staff were sent from Nairobi to assist, and on 17 February 1977 WHO epidemiologists well acquainted with surveillance and outbreak investigation arrived. Mass vaccination carried out by 6 teams with vehicles in villages and towns accessible by road had commenced on 28 January. By mid-February, the proportion of the population vaccinated reached 80% in the main villages, but only 30% in more remote villages. In fact, the 16 inhabitants of a village located just 2 kilometres from the outbreak were found, in early March, not to have been vaccinated at all. Meanwhile, because of heavy rains in the area, many nomads began moving through the area from Ethiopia as well as Somalia. At the end of April, a survey of 2256 persons in a nearby division revealed that only 527 (23%) had vaccination scars. By the end of February, a search had been organized throughout the eastern part of Mandera District which, by assessment, was reasonably effective. A reward of 200 Kenya shillings (US$24) was offered to anyone reporting a case. Gradually, monthly searches were extended to other districts bordering on Ethiopia and Somalia, but because of mud, vehicle breakdowns and scarcity of staff, probably not more than a half to two-thirds of the districts were satisfactorily searched. The searches continued until March 1978, some 6 months after the last known case occurred in Somalia.

It was feared that more cases would be found, but only 1 additional case was discovered by the search teams, in a 25-year-old man who had become ill on 16 December 1976. The source of infection was not

Plate 19.7. The strategy for search activities in Kenya during 1977 was worked out by Jean-Paul Ryst (b. 1939), a WHO consultant, Ziaul Islam (b. 1931), a WHO medical officer for epidemiological surveillance in Africa, 1971–1982, and Wilfred Koinange (b. 1939), Director of Health Services of Kenya.

determined although it was considered to be unrelated to this outbreak. Meanwhile, efforts were made to find the original case in Somalia but it was never discovered.

CONCLUSION

The circumstances attendant on the eradication of smallpox from these 5 countries were wholly unlike those encountered in Asia or South America. In Asia, levels of vaccinial immunity comparable with, and in many instances better than, the levels observed in eastern Africa failed to stop transmission. Only when a fully effective surveillance–containment programme was introduced could transmission be interrupted. In Brazil, surveillance and containment played a notably less important role in eradication, but there the vaccination campaign was carefully executed with specially trained assessment teams evaluating the performance of the vaccination teams on a daily basis. In Kenya, Uganda, and Tanzania, smallpox incidence was diminishing rapidly by the time the Intensified Programme began. In all but limited areas of Tanzania, and in Rwanda and Burundi, the introduction of freeze-dried vaccine of good quality was all that was required to interrupt transmission; the extensive infrastructure of health services did the rest. Mass vaccination campaigns, with neither assessment nor surveillance (except in Rwanda), served to eliminate smallpox in the other areas.

Whatever the deficiencies of the programmes, smallpox transmission was rapidly interrupted at little cost, with the addition of only a few experienced health staff, a small cadre of minimally trained vaccinators and encouragement and support from WHO. In retrospect, many factors account for this success: the substitution of freeze-dried for liquid vaccine; the ready, even enthusiastic, acceptance of vaccination by most of the population; the good cooperation of village leaders, missionaries, teachers and others; the presence of milder strains of variola virus which spread less easily; the generally sparse population and the infrequency with which they travelled over long distances; and an extensive network of health centres and clinics, many of which undertook to control outbreaks when these were discovered.

Of particular note in these countries was the extraordinarily high productivity of the staff compared, for example, with that of their counterparts in the Indian subcontinent. Whereas in the latter group of countries, the performance of 25 vaccinations by a vaccinator in one day was considered to be a worthy accomplishment, African vaccinators regularly vaccinated on average 500 or more individuals a day, the record being achieved in Rwanda, where during a particular month,

the vaccinators, using bifurcated needles, averaged 1508 vaccinations per vaccinator per day. In the Indian subcontinent, it was considered necessary to have at least 1 smallpox vaccinator for every 5000–8000 or 20 000 persons, according to circumstances. In the countries of eastern Africa, on the other hand, the total smallpox eradication staff, at maximum strength, numbered only 1 per 148 000 persons in Kenya, 1 per 180 000 in Tanzania and 1 per 136 000 in Rwanda.

The rapidity with which success was achieved in these and other African countries, at such little cost and with minimum effort, provided enormous encouragement to the global eradication programme. To have interrupted transmission in countries in which health services were considered to be less effective and extensive than in Asia was an important factor in motivating Asian governments to make a more concerted attack on the problem.

CHAPTER 20

SOUTHERN AFRICA

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INTRODUCTION

In southern Africa, 10 countries or political jurisdictions lie south of Zaire and the United Republic of Tanzania, occupying an area of 6 million square kilometres (Fig. 20.1). This land mass consists principally of a great central plateau, primarily temperate to subtropical in climate; in 1970 its estimated population amounted to 54 million. The vast deserts of the Namib and Kalahari in the west encompass much of Namibia and Botswana, giving way to undulating plains and savanna to the east and eventually to detached groups of hills and mountains which extend from Malawi through western Mozambique and eastern Zimbabwe (called Southern Rhodesia prior to 1980).

In 1967, when the Intensified Smallpox Eradication Programme began, smallpox throughout southern Africa did not appear to be a major problem. Four areas—Angola, Botswana, Lesotho and Namibia—were believed to be non-endemic; 6 other areas recorded a total of only 534 cases in 1966 and 262 in 1967. Health services in most parts of southern Africa were generally more extensive than elsewhere in the continent and all had some type of organized programme of smallpox vaccination. Although smallpox was undoubtedly a greater problem than official data conveyed, it was thought to be not as widespread or of such high incidence as in neighbouring Zaire or the United Republic of Tanzania, for example.

Given the status of smallpox and the national resources available in many of the countries, prospects for the early interruption of smallpox transmission throughout this vast area might have appeared hopeful. However, political problems made it difficult for WHO to cooperate with the authorities in large parts of southern Africa, and these constraints inhibited the programme. Only 4 countries, with a total population of 10.4 million (in 1970), were Member States of WHO with full voting rights (Table 20.1). A fifth, Swaziland, became independent in 1968 and joined WHO a few years later. Official contact between the Organization and the health authorities of the other 5 political jurisdictions, which had a total population (in 1970) of 42.8 million, was difficult at best and in certain cases practically nonexistent. Angola and Mozambique, both Overseas Provinces of Portugal until 1975, were preoccupied with a

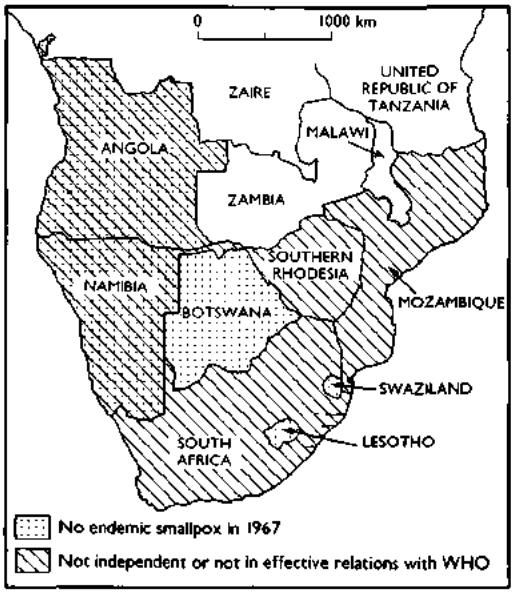


Fig. 20.1. Southern Africa: countries and territories, smallpox endemicity, and relationship with WHO, 1967. The endemicity shown reflects the situation in 1967 as determined later.

protracted and costly civil war. Contact with their health authorities had to be made through the government in Lisbon, for which smallpox eradication was an issue of little significance compared with other problems. Namibia (South West Africa) was administered by South Africa, which, though still a WHO Member State, had been deprived of voting privileges and services by the Seventeenth World Health Assembly in 1964 and which had subsequently ceased to pay its annual contribution or to attend the World Health Assembly. Communications between WHO and South Africa all but ceased at this time, along with South Africa's participation in the Organization's activities. Until 1965, Southern Rhodesia had been an Associate Member of WHO, being represented by the United Kingdom in its international relations. When the government unilaterally declared independence, its rights were suspended on the initiative of the United Kingdom. Communications between WHO and Southern Rhodesia had officially to be conducted through the government in London, but there was little or no official contact between the United Kingdom and the new government of Southern Rhodesia.

The only permissible contact between WHO and the 5 above-mentioned political jurisdictions was embodied in the provisions of the International Health Regulations, which required each to report weekly to WHO Headquarters the number of cases of smallpox, as well as other stipulated "quarantinable diseases", and the areas that were affected. WHO Headquarters, in turn, could query reports and transmit information deemed to be of importance in the control of these diseases. Although many of the authorities concerned, like those of some other countries, were neither prompt nor comprehensive in their reporting, this contact, tenuous as it was, proved to be an important one.

A further difficulty lay in the fact that smallpox eradication held little interest for South Africa, in which an especially mild form of variola minor was prevalent, the severity of which was comparable to that of chickenpox.

In the circumstances, WHO could freely communicate with and provide assistance only to its "active" Member States, which together accounted for just 20% of the population of southern Africa. It was hoped that in the other endemic areas, programmes would eventually be conducted, if for no other reason than to avoid opprobrium in the eyes of independent African governments which had succeeded in eradicating smallpox.

It was therefore difficult to assess the extent of endemic smallpox in most countries of southern Africa between 1967 and 1971, not only because of problems of communication

Table 20.1. Status of political jurisdictions in southern Africa, 1967–1975

	Population in 1970 (thousands)	Area (km^2)
WHO Member States:		
Botswana	623	600 372
Lesotho	1 064	30 355
Malawi	4 518	118 484
South Africa[a]	22 760	1 221 037
Swaziland	426	17 363
Zambia	4 189	752 614
Political jurisdictions administered by other countries:		
Angola	5 588	1 246 700
Mozambique	8 140	799 380
Namibia	1 042	824 292
WHO membership in suspense:		
Southern Rhodesia	5 308	390 580

[a] Deprived of voting privileges and services in 1964.

but also because the completeness of notification improved only slowly during this period. Few outbreaks in any country were investigated by appropriately trained staff or were confirmed by laboratory diagnosis. As a consequence, the extent of underreporting, the numbers of reported cases and outbreaks that represented importations from other countries, and the numbers of cases of chickenpox that might have been misdiagnosed as smallpox were, and remain, a matter of conjecture.

Mass vaccination campaigns, assisted by WHO, were conducted in Botswana, Malawi and Zambia; similar campaigns, assisted by WHO and UNICEF, were carried out in Lesotho and Swaziland. None, except the Botswana campaign, was particularly well executed. Nevertheless, transmission was interrupted in Zambia in 1968 and in Swaziland in 1966 or 1969, as is discussed later in this chapter. In Malawi, the disease disappeared in 1971. Lesotho's last cases had occurred in 1962, 5 years before the beginning of the Intensified Programme.

Of the 5 political jurisdictions in southern Africa referred to earlier, Angola and Namibia remained smallpox-free, but endemic smallpox was present in 1967 in the other 3—Mozambique, South Africa and Southern Rhodesia. Because of political constraints, they received no help from WHO in their programmes. Mozambique conducted an extensive vaccination campaign in areas accessible to the health authorities, and in February 1969 the last cases were detected. Southern Rhodesia recorded small numbers of cases throughout 1970, all of them along its eastern border with Mozambique. The last known case occurred in December 1970, but whether it was the last in a continuing chain of endemic transmission or a result of importations from remote areas of Mozambique or Malawi remains unknown. South Africa began active eradication measures in 1970, conducting extensive systematic vaccination campaigns in northern parts of Transvaal Province, its only known endemic area. In 1971, it recorded its last indigenous case.

From February to August 1971, no cases of smallpox were reported to WHO from any country in southern Africa. Just when hope was growing that smallpox had been eliminated from this large area, cases began to be reported from Botswana, a hitherto smallpox-free country, adjacent to South Africa's Transvaal Province. During the preceding 6 years, only a single imported case had been detected in Botswana. Vaccinial immunity throughout the country was low and smallpox began to spread. This was alarming. Not only might smallpox again become established in a country that had been free from it, but it was feared that it might spread through the populated areas in north-western Botswana into areas of Angola which were inaccessible because of civil war. If smallpox were to become re-established there, the prospects for eradication would be significantly diminished. Effective measures to control the disease were greatly delayed but, by good fortune, it remained confined to Botswana, in which more than 1000 cases were recorded during 1972 and transmission persisted until November 1973.

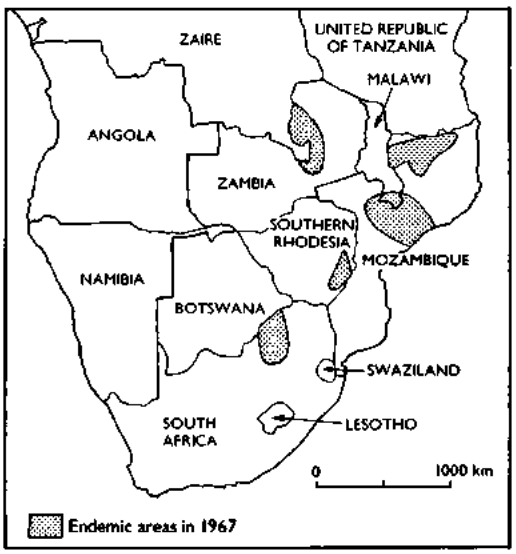


Fig. 20.2. Southern Africa: probable extent of endemic smallpox, 1967.

On the basis of a retrospective review of data collected during the course of the programme and, subsequently, during activities leading to certification, it is probable that in 1967 there were not more than 5 comparatively small foci of smallpox (Fig. 20.2). One was in Zambia in areas adjacent to the then heavily endemic Katanga (Shaba) Province of Zaire. A second straddled the Mozambique–United Republic of Tanzania border, where a Mozambican independence movement was centred and where military forces associated with this movement, as well as refugees, moved into and out of the United Republic of Tanzania. A third lay in central

Mozambique and southern Malawi, likewise an area in which security was a problem; a fourth was in rural mountainous areas of Southern Rhodesia and may or may not have extended into adjacent areas of Mozambique; the fifth was in Transvaal Province of South Africa. In all areas except South Africa, smallpox with a case-fatality rate of 5–15% prevailed; in South Africa, a very mild form of variola minor was present with a case-fatality rate of less than 1%.

In this sparsely populated region of Africa, smallpox was readily interrupted with national or regional mass vaccination campaigns, few of which are believed to have achieved the high levels of vaccinial immunity attained in Zaire and western Africa. Moreover, except in Botswana, programmes of surveillance and containment were never well developed. However, the eradication programme served in some countries to develop reporting systems and to promote routine vaccination against this and other diseases in existing health facilities. It is apparent in retrospect, though, that eradication might have been achieved more readily and more rapidly if freeze-dried vaccine had been supplied to existing health programmes and if simple surveillance activities had been developed.

This chapter discusses first the activities in Zambia and then the programmes in Malawi, Mozambique and Southern Rhodesia. A third section deals with smallpox in the adjacent countries of South Africa, Botswana, Lesotho, Namibia and Swaziland. Lastly, activities in smallpox-free Angola are briefly described.

Table 20.2. Zambia: number of reported cases of and deaths from smallpox and case-fatality rates, 1956–1973, and number of vaccinations performed, 1964–1973

Year	Number of cases	Number of deaths	Case-fatality rate (%)	Number of vaccinations[a]
1956	576	52	9.0	..
1957	459	56	12.2	..
1958	210	21	10.0	..
1959	178	13	7.3	..
1960	350	31	8.9	..
1961	233	8	3.4	..
1962	210	4	1.9	..
1963	1 881	271	14.4	..
1964	2 214	189	8.5	1 657 330
1965	528	59	11.2	1 500 000
1966	63	10	15.9	1 535 634
1967	47	3	6.4	1 183 836
1968	33	5	15.2	1 365 514
1969	0	–	–	1 508 958
1970	2[b]	–	–	1 525 511
1971	0	–	–	1 549 479
1972	0	–	–	1 400 000
1973	0	–	–	1 500 000

[a] .. = data not recorded.
[b] Imported from Zaire.

ZAMBIA

Zambia, a subtropical country consisting largely of wooded plateau, became independent in 1964. Its population of 3.8 million (in 1967) lived primarily in scattered villages, only 700 000 being resident in the 9 major towns. Its road system was comparatively extensive, as was its network of health facilities, which included 60 hospitals, 93 urban and specialized clinics and 323 rural clinics. Many of these were staffed by expatriates, there being at that time only 3 Zambian physicians and a dearth of Zambian paramedical staff. Few of these health units, however, provided vaccination against smallpox.

Smallpox, with a case-fatality rate of 5–15%, similar to the form existing in neighbouring Zaire, had been prevalent for many years (Table 20.2). Mass vaccination campaigns employing liquid vaccine were conducted during periodic outbreaks.

In 1963–1964, major epidemics began to occur in Zambia (Fig. 20.3), primarily along the Zairian border. The new government responded with a national mass smallpox vaccination campaign utilizing specially con-

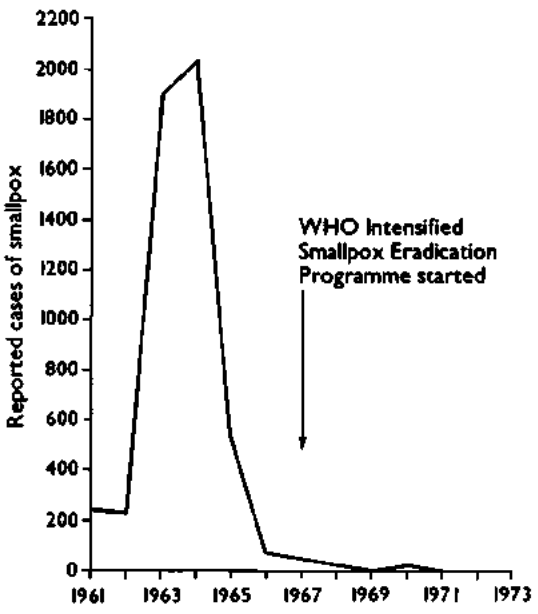


Fig. 20.3. Zambia: number of reported cases of smallpox, by year, 1961–1971.

stituted mobile teams. The programme began in 1964 in each of 8 provinces under the supervision of provincial officials. One hundred and forty vaccinators were recruited and trained locally and discharged when the team had completed its work in a given area. They vaccinated at assembly points, using liquid vaccine. The intent was to vaccinate one-third of the population of each province each year. Vaccinations were performed during the dry season, from May to November. Despite a serious shortage of transport, limited supervision and inadequate refrigeration facilities, 1.66 million vaccinations were reported to have been given during 1964 and 1.5 million in 1965. Take rates among primary vaccinees were found to be about 80%. This was lower than the take rates expected when freeze-dried vaccine was used but, considering the logistic problems in the country, it was a remarkably good result. The number of reported cases decreased sharply, from 2214 in 1964 to 528 in 1965.

In January 1966, freeze-dried vaccine, donated by the USSR, began to be employed. That year, another 1.54 million persons were vaccinated, and the number of cases decreased further to only 63 in 1966.

The government was committed to smallpox eradication and in March 1967 requested WHO to provide vehicles, refrigerators and other equipment as well as 4 advisers—a medical officer counterpart for the director and 3 operations officers to serve in supervisory roles, where needed, at provincial level. Between 1967 and 1973, WHO was to provide 10.6 million doses of vaccine and expend US$644 146, an outlay which included WHO salary payments. The WHO medical officer arrived in November 1967 and the 3 operations officers in 1968. Meanwhile, the government staff for the mass vaccination campaign was increased from 140 to 207.

Under the new WHO-assisted programme, BCG vaccine was given simultaneously to all schoolchildren and, in two of the provinces, to younger children as well. Between January 1966 and the end of 1968, the so-called "first phase" of the programme was completed—i.e., vaccination with freeze-dried vaccine throughout the country. The number vaccinated was roughly equivalent to the estimated population. In 1968, only 33 cases were reported and smallpox transmission appears to have been interrupted in December of that year.

During 1967–1968, the WHO-assisted programme changed little in character. Vaccination was conducted at assembly points; coverage and take rates were assessed only occasionally; little was done to improve the surveillance system. Indicative of the quality of surveillance is the fact that little is known about the last 10 cases reported in 1968, except that 2 were said to have been infected in Zaire.

Beginning in 1968, the established government health units were provided with stocks of vaccine and encouraged to vaccinate all who attended but, as was true in many countries, these units evinced little interest in undertaking even this most simple of preventive measures. Throughout the whole of 1969, they performed only 91 650 vaccinations and many of these were given by programme vaccinators who were assigned to clinics. Fully 3 additional years of concerted effort were required before the staff of the health units began to vaccinate significant numbers of persons.

Although a programme of vaccination had been completed throughout the country, the government decided in 1969 to repeat the national mass vaccination campaign, using special teams as before. Because smallpox was still endemic in neighbouring Zaire, the United Republic of Tanzania and Mozambique and because the existing health units were providing little help, government officials felt that this was the only way that they could ensure a sufficiently high level of vaccinial immunity to prevent spread should introductions occur.

The WHO operations officers were assigned to the provinces bordering on Zaire, and vaccination check-points were established at the principal border crossings to examine persons entering the country and to vaccinate anyone without a scar. In some areas, the coverage achieved was assessed by WHO operations officers after the teams had worked in an area. Throughout Zambia, however, supervision generally remained poor, which was reflected in the unsatisfactory performance of vaccinators, who averaged only 40 vaccinations per day.

The repeat mass vaccination campaign was costly but it did assure the movement throughout the countryside of vaccination teams which could detect any cases that existed. Between 1969 and 1971, an additional 4.6 million vaccinations were performed, the annual average being no more than had been

achieved in 1964–1965, before the provision of WHO assistance.

During 1970, at the midpoint of this repeat round of mass vaccination, a cluster sample survey of the country was carried out by staff of the WHO Epidemiological Surveillance Centre in Nairobi, Kenya, to measure the level of vaccination coverage. In all, 17 927 persons were examined. The proportion with vaccination scars was found to range from 62% to 80% in the different provinces, but in 5 of the 44 districts it was discovered that fewer than 60% of the people had ever been vaccinated. By any standard, the programme had not been notably successful.

The need to recruit at least one experienced team to encourage reporting and to investigate each suspected case had been stressed repeatedly by Ladnyi, the WHO intercountry smallpox adviser for eastern and southern Africa, but not until late 1969 was such a team formed and the first efforts made to ensure that each of the 429 health units provided a weekly report. Even then, the effort left much to be desired: as late as June 1970 the WHO medical adviser to the national programme commented that a report of a suspected case was *usually* followed by immediate investigation. The concept that *every* suspected case was important was not understood.

Meanwhile, in Zaire, mass vaccination throughout the neighbouring Shaba Province was completed during 1969, although a few cases of smallpox were reported each month in early 1971. Despite the continuing presence of endemic smallpox just across the border, only 2 imported cases were detected in Zambia, in April 1970. These cases actually spent less than a day in the country. The individuals concerned—a 4-year-old child and a 7-year-old child—were brought across the river from Zaire by their parents to be examined at a clinic. They were diagnosed as suffering from smallpox by the staff of the clinic and were promptly sent back to Zaire, but the incident was duly reported to the provincial health office. These were Zambia's last known cases.

Not until the beginning of 1971, when the risk of importations seemed to have diminished almost to nil, was a comprehensive surveillance system finally established in northern Zambia, near the borders with Zaire and the United Republic of Tanzania. In these areas each village was visited twice monthly by a surveillance agent to detect cases with rash and fever which might be smallpox. Additional permanent vaccination posts were established along the frontiers and many suspected cases were investigated. Because the United Republic of Tanzania detected no cases in 1971 and Zaire found none after June of that year, it is not surprising that no further cases were discovered in the bordering areas of Zambia.

With the conclusion of the second round of mass vaccination, the number of staff was reduced and the number of WHO advisers decreased from 4 to 2. A maintenance programme was established whereby 15 mobile vaccination teams moved through the provinces vaccinating the more remote populations and encouraging vaccination in established health facilities. In all, 1.4 million persons were vaccinated in 1972 and 1.5 million in 1973, numbers comparable to those vaccinated by the much larger special vaccination campaign staff. In the mid-1970s, immunization against several diseases began to be offered by many of the established health units, and monthly reports giving the number of cases of disease and the number of vaccinations performed were received regularly from 96 hospitals and 689 health centres and subcentres.

The age distribution of cases during 1964–1965 was unusual in that 86% of those recorded were in individuals aged less than 6 years (Table 20.3). This was an unusually high proportion of cases among young children,

Table 20.3. Zambia: age distribution of reported cases of smallpox, 1964–1965 and 1966–1968

1964–1965			1966–1968		
Age group (years)	Number of cases	%	Age group (years)	Number of cases	%
<1	626	23	<1	40	28
1–5	1 733	63	1–4	63	44
6–14	257	9	5–14	26	18
⩾15	126	5	⩾15	14	10
Total	2 742	100	Total	143	100

for which there is no explanation other than that it may have been an artefact of reporting. Data for the 1966–1968 period show a more typical age distribution of cases.

MALAWI, MOZAMBIQUE AND SOUTHERN RHODESIA

Background

Malawi, Mozambique and Southern Rhodesia together had a population of 18 million (in 1970) and a reasonably extensive network of health centres and roads, Southern Rhodesia's being the most fully developed. From 1963, the prevalent form of smallpox in these countries appears to have been variola major, with a case-fatality rate of 5–15%. During the early 1960s, smallpox had been of special concern to the health authorities, and all had organized mass vaccination campaigns employing mobile teams. Reasonably satisfactory control seems to have been achieved. In all, only 142 cases were reported in 1966 and 172 in 1967, although the true numbers were undoubtedly much greater because notifications in these countries, as elsewhere, were very incomplete.

The recurrence of variola major was a recent development. Variola major had been prevalent before 1952, but in that year it was replaced by variola minor. From 1952 to 1958, for example, Malawi recorded 810 cases but only 8 deaths. In 1959, both the number of cases and the case-fatality rate began to increase and by 1961, 1465 cases with 161 deaths were reported (Table 20.4). The source of the strain which infected Malawi was in all likelihood either neighbouring Zambia or the United Republic of Tanzania. In Mozambique, a similar change in the prevalent smallpox strain took place in 1962–1964, at the time of civil conflict along its border with the United Republic of Tanzania. In 1963, fatal cases began to be observed in Southern Rhodesia, virtually all of them occurring in the eastern provinces bordering on Mozambique.

The civil war in Mozambique played a significant role in the persistence of smallpox in these countries. A national independence movement, which had been established in border areas in the south of the United Republic of Tanzania, moved into the 2 northern provinces of Mozambique in 1964. In addition to conducting guerrilla warfare, the independence movement established a political and administrative structure which, during the following decade, expanded into the central and north-western provinces. To combat this movement, the Mozambican government resettled many of the scattered rural population into villages which could be defended and in which health and educational services could be provided. Thus, village health units capable of reporting cases of smallpox existed throughout the country, but few activities were possible in the sparsely populated rural areas, including extensive tracts adjacent to the United Republic of Tanzania, Malawi and Southern Rhodesia.

Table 20.4. Malawi, Mozambique and Southern Rhodesia: number of reported cases of and deaths from smallpox and case-fatality rates, 1959–1972

Year	Malawi			Mozambique			Southern Rhodesia		
	Number of cases	Number of deaths	Case-fatality rate (%)	Number of cases	Number of deaths	Case-fatality rate (%)	Number of cases	Number of deaths	Case-fatality rate (%)
1959	559	23	4.1	44	0	0	133	0	0
1960	795	64	8.1	14	0	0	12	0	0
1961	1 465	161	11.0	91	2	2.2	3	0	0
1962	634	69	10.9	69	4	5.8	15	0	0
1963	455	57	12.6	102	7	6.9	38	5	13.2
1964	720	55	7.6	243	24	9.9	200	15	7.5
1965	226	8	3.5	115	25	21.7	40	3	7.5
1966	88	2	2.3	19	6	31.6	35	0	0
1967	38	3	7.9	104	32	30.8	30	1	3.3
1968	61	7	11.5	145	15	10.3	10	1	10.0
1969	65	4	6.2	11	0	–	33	2	6.1
1970	39[a]	1[a]	2.6	0	–	–	6	0	–
1971	10[b]	0	0	0	–	–	0	–	–
1972	0	–	–	0	–	–	0	–	–

[a] Cases documented during survey in 1972.
[b] Nine cases documented during 1972 survey and 1 during 1977 survey.

Vaccination Campaigns

For a number of years prior to 1967, a considerable proportion of the population in each country was reported to have been vaccinated each year (Table 20.5), but none of the programmes incorporated a system for assessing the level of coverage achieved, and only in Southern Rhodesia were take rates regularly appraised.

Freeze-dried vaccine was used only in Mozambique, the vaccine having been produced at the Instituto de Investigação in Lourenço Marques (now Maputo). Samples of this vaccine were tested by the International Reference Centre for Smallpox Vaccine in Bilthoven, Netherlands, in 1968 and 1972 and found to meet WHO standards. Vaccination in Mozambique was offered in hospitals as well as in health and first-aid posts and by mobile teams, each of 9 districts having 3 or 4 teams which sought to vaccinate one-third of the population each year. BCG vaccination was given simultaneously. During 1968, a special campaign was conducted which succeeded in vaccinating against smallpox half of the 8 million residents, although, because of security problems, 2 districts in the north, Niassa and Tete, could not be well covered. A repeat campaign was conducted in 1972, during which, because hostilities had subsided in Tete District, it was possible to vaccinate most of the people in this area. Although the coverage was not assessed, vaccinial immunity was probably reasonably good among accessible populations, considering that a large number of people had been vaccinated and freeze-dried vaccine had been used. However, immunity was undoubtedly much lower among the inhabitants of the large sparsely populated rural areas of the central and northern parts of the country.

In Southern Rhodesia, a similar type of programme was conducted, with vaccination being given by mobile teams and in existing health facilities. Poliomyelitis and BCG vaccines were administered simultaneously to children. Until 1970, liquid smallpox vaccine produced in South Africa had been employed. A continuing assessment of take rates among primary vaccinees was conducted by local health authorities, and these showed 75–90% successful vaccinations—rates which were lower than those obtained with freeze-dried vaccine, but higher than those in most countries that used liquid vaccine. The only available data regarding the prevalence of vaccinial immunity are from a 1978 government survey, which found that 74% of children aged 1–6 years and 92% of those aged 7–10 years had vaccination scars.

In Malawi, a permanent staff of 42 vaccinators regularly travelled by bicycle through their assigned regions, giving smallpox vaccine only; a 10-man mobile team was available for vaccination where outbreaks occurred. The mobile team worked primarily in the south, where, after 1965, almost all cases were found. Until 1966, liquid vaccine was employed; primary take rates, when measured in the field, were only 25–50%. The programme was not particularly successful, as was apparent from a survey in 1965, which showed that only 360 of 2566 schoolchildren (14%) in and around the capital city had vaccination scars. In January 1966, freeze-dried vaccine was made available by UNICEF and thereafter only this type of vaccine was employed. WHO staff visiting the country in 1966 and 1968 found that the supervision of vaccinators was poor, their productivity was low and the vaccinial immunity of the population was unsatisfactory. In one area of southern Malawi, in which United States Peace Corps volunteers assisted in mass vaccination in 1968, 50% of the inhabitants remained unvaccinated at the end of the campaign. Late in 1969, the government decided to request assistance from WHO in conducting a national smallpox eradication programme, but a better-organized vaccination campaign did not begin until April 1972. That programme included the administration of both BCG and smallpox vaccines. When the campaign was launched, surveys in different areas showed that 30–60% of children aged 0–4 years and 36–76% of those aged

Table 20.5. Malawi, Mozambique and Southern Rhodesia: number of reported vaccinations performed, 1964–1973

Year	Number of vaccinations (% of total population)		
	Malawi	Mozambique	Southern Rhodesia
1964	1 569 000 (40)	1 056 726 (15)	2 495 112 (59)
1965	751 413 (19)	2 139 489 (29)	1 371 600 (31)
1966	832 201 (20)	1 463 938 (20)	1 109 997 (24)
1967	675 390 (16)	2 433 705 (32)	1 173 216 (25)
1968	768 000 (18)	4 111 960 (53)	1 144 930 (23)
1969	970 161 (22)	977 281 (12)	977 073 (19)
1970	1 265 335 (28)	1 234 986 (15)	1 198 282 (23)
1971	525 329 (11)	2 195 546 (26)	1 399 552 (26)
1972	562 347 (12)	2 379 761 (27)	1 401 168 (25)
1973	489 111 (10)	2 533 968 (28)	1 119 614 (19)

5–14 years had vaccination scars. Only 5 months after the programme had begun, it was stopped by the government on account of the occurrence of abscesses due to BCG vaccination. It did not recommence until August 1973—almost a year later—but was halted once again, in December 1973, when cholera broke out and the teams were reassigned to perform cholera vaccination.

Finally, in 1974, an extensive vaccination campaign began, long after the last cases had been detected. It concluded in 1976. WHO financial support throughout the course of the programme amounted to US$311 011; in addition, 7.8 million doses of vaccine were supplied.

The Smallpox Situation

In the 3 countries under review, information about smallpox, from 1967 until 1971, when the last known cases were detected, is sketchy. Undoubtedly, many cases occurred which were not reported and some which were reported may not have been smallpox. Health authorities at district or provincial level in each country usually performed area-wide vaccination when cases were reported but rarely did they conduct investigations to detect additional cases or to identify the source of infection. Ladnyi, during visits to Malawi, tried to persuade the government to initiate a surveillance programme, but not until 1973 was a satisfactory programme established for the investigation of suspected cases of smallpox. Since there could be no direct official communication between WHO and the health authorities in Mozambique and Southern Rhodesia, a similar effort to encourage proper surveillance in these areas was greatly delayed. At the end of 1969, some WHO staff began corresponding personally with university faculty members in Salisbury, Southern Rhodesia, who soon thereafter undertook to examine specimens from many suspected cases although few epidemiological investigations were conducted. Not until the spring of 1972 did WHO and the countries concerned reach agreement to give Henderson special permission to visit Mozambique (as well as Angola and South Africa although not Southern Rhodesia) to assess the nature of their programmes and to discuss needed surveillance measures in areas then believed to be smallpox-free. Information about smallpox, even that pertaining to the last outbreaks, is thus fragmentary in all the countries concerned.

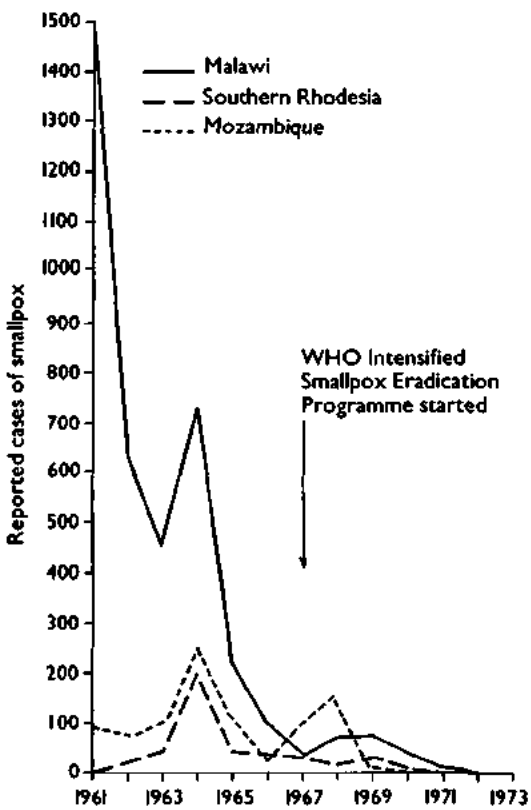


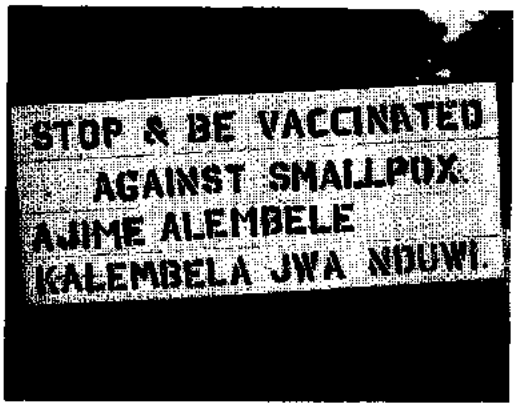
Fig. 20.4. Malawi, Mozambique, Southern Rhodesia: number of reported cases of smallpox, by year, 1961–1972.

Mozambique detected 104 cases in 1967, 145 in 1968 and 11 in 1969 (the last occurring in February) (Fig. 20.4). Of the 145 cases in 1968, 142 were reported from parts of only 3 provinces, all in the north of the country (Fig. 20.5). Most of the outbreaks occurred in villages in Tete District, near the border with Malawi, and in Niassa District, which adjoined endemic areas in the United Republic of Tanzania. The 11 cases detected in 1969 were all in Niassa District. Because the guerrilla forces of the independence movement continued to travel between Niassa and the southern part of the United Republic of Tanzania, it is possible that these foci were related. This is speculation, however, since in neither country were outbreaks investigated to determine their sources. Few smallpox cases were reported in the south of the United Republic of Tanzania after 1969 but it later became apparent that the disease persisted in

border areas of Malawi and Southern Rhodesia, at least until the end of 1970. In Mozambique, however, no further cases were detected after 1969. Because security in many of the border areas was problematic, cases may well have occurred but remained undetected.

In Malawi, all cases after 1966 were reported from the south of the country. Southern Malawi presented an especially difficult problem. Large numbers of refugees from Mozambique lived in the region, most of whom crossed into the country through forest areas rather than at official border crossings. As illegal immigrants, they sought to avoid any contact with government authorities and often fled into the jungle when teams came to vaccinate. In order to contain outbreaks, villages were sometimes surrounded by a police cordon to prevent villagers from leaving the area until all had been vaccinated. In addition, some outbreaks were discovered during which variolation had been performed, supposedly in order to quell the spread. Cases which were detected were frequently reported as occurring among refugees from Mozambique or residents who had been in contact with them. Whether the cases represented new importations or continuing transmission among immigrants is unknown. Malawi reported only 61 cases in 1968 and 65 cases in 1969. In December 1969, the last case was reported by the health services. No cases were notified during 1970–1971.

By early 1972, it appeared that smallpox transmission might have ceased in the Malawi–Mozambique area. More than a year had elapsed since the last cases had been detected in Malawi and nearly 3 years since the last case had been reported in Mozambique. However, neither country was believed to have adequate surveillance programmes



I. D. LADNYI, 1967

Plate 20.1. Important foci of smallpox in southern Africa were situated along the border between Mozambique and Malawi, which was frequently crossed by Mozambicans fleeing the civil war. They were stopped and vaccinated if they used the official crossing points, but most went along forest trails and so escaped vaccination.

and thus doubts persisted as to whether smallpox was really absent. WHO staff could not participate in confirmatory studies in Mozambique but they could do so in Malawi. In April 1972, Dr Ziaul Islam, who had replaced Ladnyi as the WHO intercountry smallpox adviser, undertook a village-by-village field survey in areas of southern Malawi in which smallpox outbreaks had repeatedly occurred between 1966 and 1969. In 5 villages, he discovered 48 individuals with facial pockmarks who had developed smallpox in 1970 and 1971 (Table 20.6). The area was densely forested, populated with many refugees from Mozambique, including groups which, for religious reasons, refused vaccination. The first case that he could identify in the chain of transmission had

Table 20.6. United Republic of Tanzania, Malawi, Mozambique and Southern Rhodesia: number of cases of smallpox, by 3-month period, 1968–1971

	1968				1969				1970[a]				1971[a]
	Jan.–March	April–June	July–Sept.	Oct.–Dec.	Jan.–March	April–June	July–Sept.	Oct.–Dec.	Jan.–March	April–June	July–Sept.	Oct.–Dec.	Jan.–March
United Republic of Tanzania	180	116	93	66	31	30	22	34	3	23	6	0	0
Malawi	29	6	10	16	28	21	9	7	0	(27)	(9)	(3)	(10)
Mozambique	8	26	45	66	11	0	0	0	0	0	0	0	0
Southern Rhodesia	2	5	3	0	4	0	14	15	0	0	1	5	0

[a] () = Cases by month of onset, discovered during 1972 and 1977 surveys.

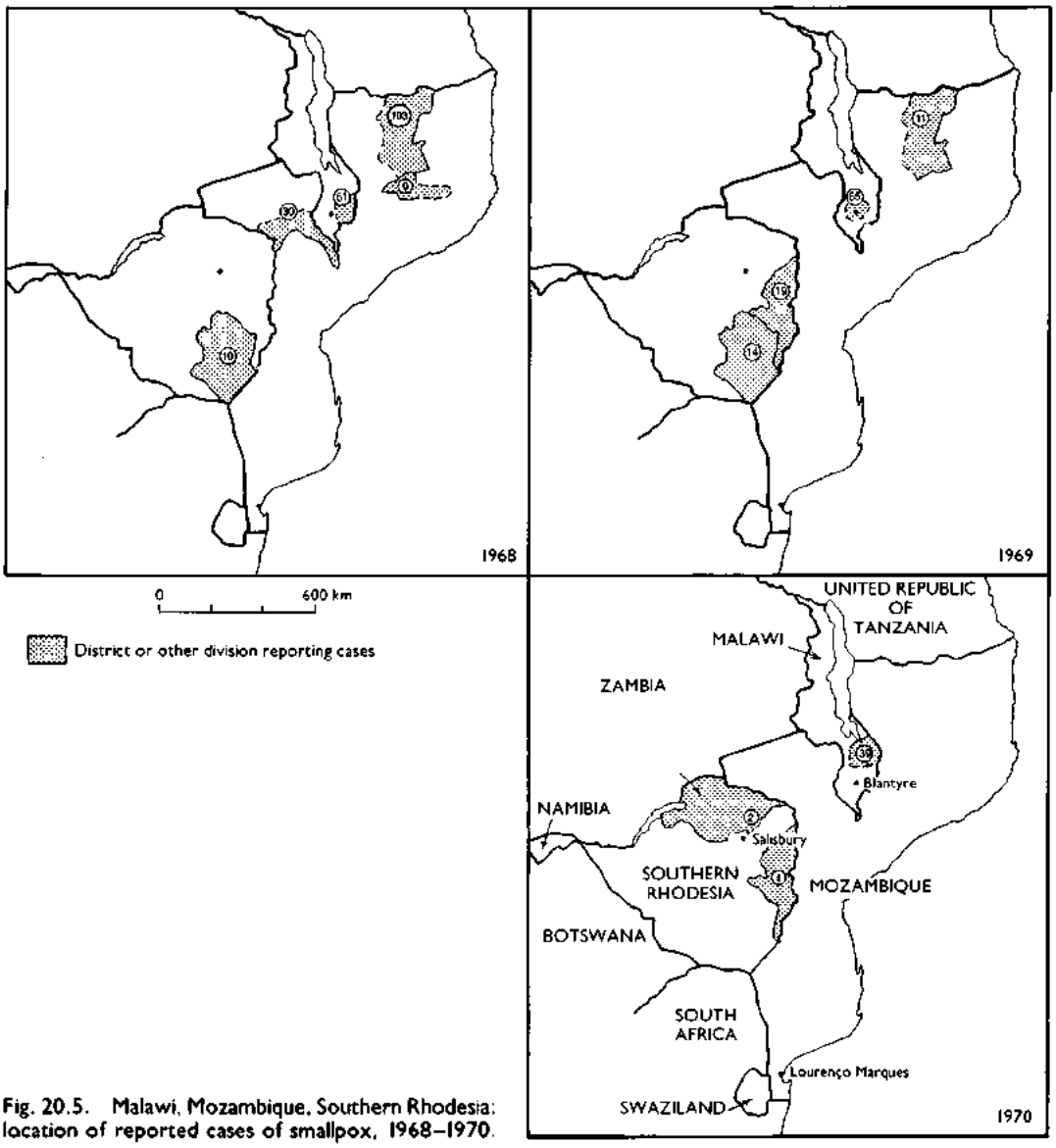
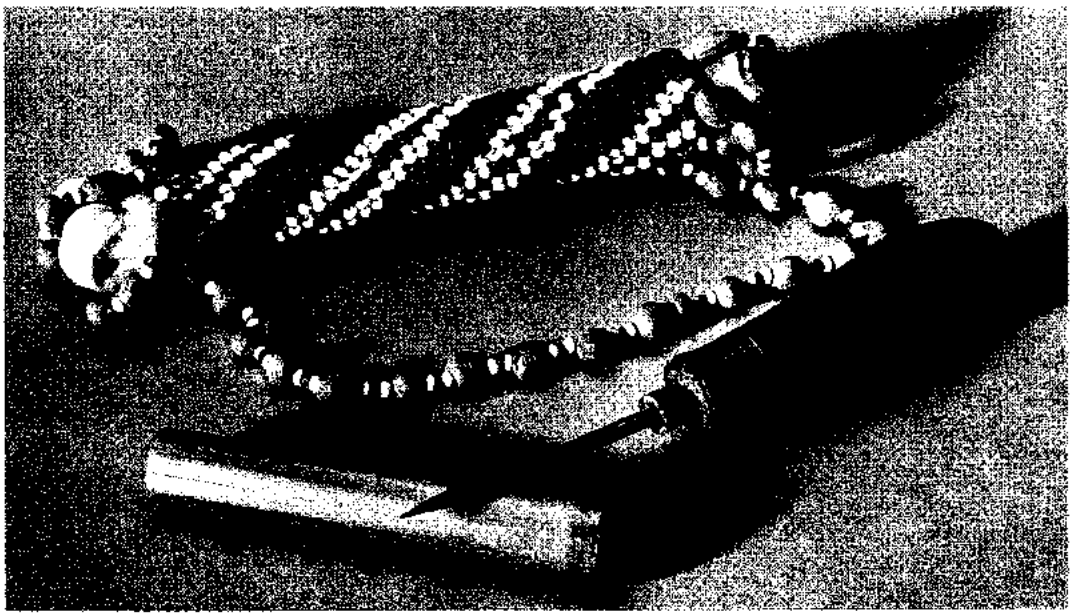


Fig. 20.5. Malawi, Mozambique, Southern Rhodesia: location of reported cases of smallpox, 1968–1970.

become ill in April 1970, and the last in February 1971. The earliest source of infection could not be specifically linked to previous outbreaks in Malawi although outbreaks had occurred in the same area in the past. During a vaccination scar survey in the affected area, Dr Islam found that 61% of children under 4 years of age, 84% of those aged 5–14 years, and 67% of persons aged 15 years and over had vaccination scars. Because of the proximity of the villages to Mozambique, the authorities there were notified. Mozambican teams subsequently undertook an extensive programme of vaccination and search throughout the adjoining area in Mozambique but found no cases. During 1977, WHO and Malawian staff undertook a more extensive survey of the entire affected area in Malawi. They confirmed Dr Islam's earlier report but failed to detect further spread. They did, however, discover a pockmarked girl who was said to have become ill in September 1972, 19 months after the presumed last case in February 1971. Extensive investigation failed to reveal any other cases among family contacts and eventually it was concluded that the reported year of illness was erroneous. Malawi's last known case is



I. D. LADNYI

Plate 20.2. Variolator's kit obtained in 1966. Scabs and pustular material were carried in the bamboo stick; the awl was used for inoculation. Malawi was the only country in southern Africa where variolation was still being practised in the 1960s.

thus thought to have occurred in February 1971 in an outbreak which terminated spontaneously without being detected by health staff.

Southern Rhodesia's surveillance programme was little better than the corresponding programmes in Malawi and Mozambique, and the origin of its last outbreaks no less mysterious. Southern Rhodesia reported only 10 cases in 1968 (Victoria Province) and 33 in 1969 (19 in Manicaland Province and 14 in Victoria Province). The outbreaks were all within 100 kilometres of the border with Mozambique. Mass vaccination was reported to have been performed in the area of each outbreak but only occasionally did provincial medical officers investigate outbreaks to ascertain the sources of infection. Indeed, as a review of records in 1978 was to show, none of the cases occurring in 1969 was investigated to determine the source of infection; a report of 10 cases was found which had been received by the provincial medical officer but had not been transmitted to the national authorities. (These cases do not appear in the official records and are not included in Table 20.4 or Table 20.6.)

In 1969, Dr Keith Dumbell from the WHO Collaborating Centre for Poxvirus Research in London and Henderson from Geneva began to correspond with Dr J. G. Cruickshank, a virologist at the University College in Salisbury, to encourage the taking of specimens from cases to confirm the diagnosis and to obtain virus strains for laboratory study. Subsequently, in March 1970, the Secretary of Health of Southern Rhodesia directed provincial medical officers to obtain such specimens, and Dr Cruickshank, employing electron microscopy and standard virus isolation techniques, began to process a flow of specimens (Swanepoel & Cruickshank, 1972). Throughout most of 1970, some of the specimens submitted showed herpes–varicella virus but none showed any poxviruses. No cases were reported to WHO from Southern Rhodesia during 1970 until 13 August, when a telex

Table 20.7. Malawi: number of reported cases of smallpox, by age group, 1960–1965[a]

Age group (years)	Number of cases	%
<6	2 079	72
6–15	528	18
⩾16	266	9
Total	2 873	99

[a] Data by age group not available for 1422 other cases reported during this period.

from the government was received in Geneva reporting a case of smallpox. Because the notification had been made under provisions of the International Health Regulations, official inquiry to Southern Rhodesia was permitted: "Would appreciate receiving urgently further particulars on source of infection of recent smallpox case and confirmation of diagnosis. No known smallpox in recent months in eastern Africa within 325 miles of Chipinga District [the location of the case]." The reply, telexed a week later, indicated that the case had not been confirmed because the patient had left the hospital before being questioned and was thought to have returned to Mozambique. The official weekly reports from Southern Rhodesia subsequently reflected no cases; only much later was the case added to the official records.

No other cases were notified until November 1970, when the government reported, by telex, 2 further cases. The existence of these cases implied that there was a persistent focus of endemic smallpox, and undoubtedly many more cases had occurred to sustain the chain of transmission. Letters and telegrams were exchanged, but to little avail. Southern Rhodesia was eventually to record officially 6 cases in late 1970. Four were reported from Chipinga Town, 25 kilometres from the Mozambican border; 2 of them were considered to have been possible importations from Mozambique but the information available was too vague to confirm this. The remaining 2 cases were reported from another province near the border and confirmed by electron microscopic examination. Their onset occurred in December 1970. It was reported that the patients had been in Mozambique 2 weeks earlier, but again the investigation was perfunctory.

Over the succeeding 5 years, Dr Cruickshank examined 17 specimens taken from suspected cases of smallpox and others from patients with chickenpox and other rash-producing illnesses. None proved to be smallpox. During 1978, in preparation for certification, extensive pockmark surveys were conducted to detect cases that might have been missed. Only 1 case was found, which had occurred in mid-1970, some 6 months before the last 2 cases were recorded. (This case does not appear in the official records and is not included in Table 20.4 or Table 20.6)

In summary, only 6 cases of smallpox were officially reported by Southern Rhodesian health staff during 1970–1971. Later, another 49 cases were discovered during special surveys in Malawi and 1 further case in Southern Rhodesia. Such investigations as were carried out suggest that persistent transmission may have continued throughout 1970 and possibly during the early months of 1971 in border areas of Mozambique as well as in Malawi and Southern Rhodesia. At all events, the number of cases was undoubtedly substantially greater than the official records indicate.

Table 20.8. Mozambique: number of reported cases of smallpox, by age group, 1968

Age group (years)	Number of cases	%
<1	24	17
1–4	44	30
5–14	42	29
≥15	35	24
Total	145	100

Age Distribution of Cases

Information regarding the age distribution of cases is available for only a proportion of the cases from Malawi during 1960–1965 (Table 20.7) and for all of those in Mozambique in 1968 (Table 20.8).

Cases in Malawi occurred predominantly among children—a characteristic of endemic smallpox—during the period 1960–1965. In Mozambique during 1968, a larger proportion of cases was found among older persons, perhaps reflecting the fact that many cases occurred among more isolated groups living in sparsely settled areas. However, because reporting in both countries was incomplete, these data must be interpreted with caution.

SOUTH AFRICA, BOTSWANA, LESOTHO, NAMIBIA AND SWAZILAND

Background

South Africa, Botswana, Lesotho, Namibia and Swaziland are closely related geographically as well as by trade and commerce. South Africa is by far the largest of these countries, with a population of 22.8 million (in 1970).

The others had a combined population of only 3.2 million, many of whom were employed in South Africa, principally in mining, or travelled there regularly. An extensive, well-developed network of health services, roads and communication facilities extended throughout South Africa; the other countries had fewer resources of this kind.

The persistence of endemic smallpox in this part of southern Africa can be attributed primarily to the fact that, for more than 50 years, the predominant type of smallpox had been a form of variola minor which was even less severe and with a lower case-fatality rate than that in the Americas. Described first in South Africa in the late 1800s, it was known as "amaas" or "kaffir-pox" (see Chapter 5). Its mild character is illustrated by the fact that from 1922 to 1944, 9122 cases were notified in South Africa but only 17 deaths were recorded. Between 1945 and 1952, however, case-fatality rates tended to approach those associated with variola major in African countries to the north. But after 1952, variola minor again displaced variola major. From 1953 to 1971, only 13 deaths attributed to smallpox were reported, of which 11 occurred in 1964 (Table 20.9) during an outbreak of 54 cases in Port Elizabeth, Cape Province. This outbreak was attributed to an importation from Zambia. Evidence that the low case-fatality rate was not an artefact due to incomplete recording of deaths was provided when variola minor spread from South Africa to Botswana in 1971. There, cases and deaths were much more carefully documented. Of 1122 patients, only 2 died.

Table 20.9. South Africa: number of reported cases of and deaths from smallpox and case-fatality rates, 1951–1972

Year	Number of cases	Number of deaths	Case-fatality rate (%)
1951	1 434	..[a]	-
1952	80	17	21.3
1953	14	0	0
1954	7	0	0
1955	27	0	0
1956	4	0	0
1957	0	0	-
1958	0	0	-
1959	0	0	-
1960	65	0	0
1961	8	0	0
1962	103	0	0
1963	254	0	0
1964	302	11	3.6
1965	191	1	0.5
1966	256	0	0
1967	43	0	0
1968	81	0	0
1969	246	0	0
1970	121	0	0
1971	10	1	10.0
1972	1	0	0

[a] .. = data not recorded.

Continuing vaccination campaigns employing liquid vaccine produced in South Africa had been in progress in each of the countries for many decades. The programmes were intended primarily to prevent large-scale outbreaks of variola major should it be reintroduced rather than to control the relatively innocuous variola minor, against which the vaccine also provided protection.

Until 1972, little information regarding the epidemiology of smallpox and the control programme in South Africa was available to WHO. That which was available was gleaned from a monthly infectious diseases bulletin published by the government and occasional reports of outbreaks sent to WHO by the Secretary of Health, in partial conformity with the International Health Regulations. Information regarding the geographical distribution of cases would have been helpful but the reports listed cases only by month and by racial group.

Data from South Africa, such as they were, were regularly included in published reviews which appeared in the *Weekly epidemiological record*. As country after country in Africa became free of smallpox, South Africa's dubious distinction as one of only a few endemic countries became politically intolerable to its authorities. Although the disease was not a public health problem, South Africa began to take an interest in smallpox in 1970 and commenced an intensive vaccination campaign in the endemic areas. Surveillance was incomplete, and it is therefore uncertain when transmission was actually interrupted. The last known endemic case occurred on 3 May 1971.

Only a few months later, neighbouring Botswana began to detect cases. Perfunctory control measures were taken but smallpox continued to spread. Not until May 1972, almost a year later, was an adequate programme begun. By then, the disease had spread widely across the country. Smallpox persisted in Botswana until November 1973.

Lesotho, Namibia and Swaziland

Events in South Africa and Botswana are described in greater detail later in this chapter. Smallpox occurrence and programme

activities in Lesotho, Namibia and Swaziland may be briefly summarized. Namibia (population in 1970, 1.04 million) was one of the most sparsely inhabited countries in southern Africa; its last known case of smallpox was reported in 1956. Vaccination programmes employing mobile teams which administered poliomyelitis and BCG vaccines as well as smallpox vaccine were well established and had been operative for many years. Because smallpox transmission had been interrupted throughout western South Africa and Angola by 1960 and in Botswana in 1964, the risk of importations was small. Even the 1971–1973 epidemic in Botswana posed little threat because the outbreaks were concentrated in the eastern part of that country, separated from population centres in Namibia by hundreds of miles of desert. Consequently, no special activities were undertaken in Namibia during the Intensified Programme.

Swaziland was first visited by Ladnyi in 1968 and Lesotho in 1970 to assess the status of their activities and to offer such assistance from WHO as might be required. Lesotho (population in 1970, 1.06 million), after many years of freedom from smallpox, experienced an outbreak of 84 cases in 1961. The outbreak extended through June 1962, 52 cases being reported that year. No deaths occurred. In 1961, 700 000 persons were vaccinated in a 3-month mass campaign and, thereafter, mobile teams supported by UNICEF vaccinated between 50 000 and 150 000 people each year, administering liquid smallpox vaccine simultaneously with BCG vaccine. In 1970, WHO began to provide freeze-dried smallpox vaccine for the programme. No further cases were found. Swaziland (population in 1970, 426 000) began experiencing smallpox outbreaks in 1963, its first since 1950. From 1963 to the end of 1966, 182, 517, 85 and 73 cases were notified for the respective years, but only 9 deaths were reported during the entire period. How many of these were genuine cases of smallpox is unknown. Of a series of 73 cases diagnosed as smallpox by auxiliary health workers, 55 were sent to hospital but none was confirmed clinically as smallpox by the physicians who saw them. In areas in which outbreaks occurred, between 44 000 and 90 000 vaccinations were performed each year from 1963 to 1966, using liquid vaccine produced in South Africa. In September 1967, a UNICEF-assisted mass vaccination campaign began, employing BCG and freeze-dried smallpox vaccine. Between 1967 and 1972, when the mass campaign concluded, between 34 000 and 64 000 persons had been vaccinated each year. Thereafter, vaccination was performed by the health centres. A survey in 1970, 3 years after the programme had started, revealed that only 51% of persons under 15 years of age and 20% of those aged 15 and over had vaccination scars. The year in which smallpox transmission was interrupted in Swaziland is unknown. Twenty-five cases were reported to WHO in 1967, 20 in 1968, and 24 in 1969. Because of this, Swaziland was originally listed as an endemic country. However, government records reviewed during certification activities show no cases after 1966 and no one at that time could be found who knew anything about the cases that were said to have occurred between 1967 and 1969. Whether these cases represented clerical error or were indeed cases of smallpox could not be ascertained. As in most countries of southern Africa, smallpox transmission had ceased spontaneously during the course of an indifferently executed vaccination campaign. When surveillance programmes eventually began, no cases could be found.

South Africa

Richly endowed with natural resources and with a large and expanding industrial base, South Africa had many of the attributes of developed countries in temperate climates. Almost half of South Africa's population of 22.8 million (in 1970) lived in urban areas. Preventive health services were administered by regional medical directors, 2 of whom were assigned to the 2 larger provinces (Cape and Transvaal) and 1 each to the 2 smaller (Orange Free State and Natal). They, in turn, oversaw the work of medical officers of health in each local authority. The pattern of vaccination activities differed somewhat from province to province but, in general, all provided vaccine through health centres and clinics, and supplemented this in rural areas by mobile teams which performed vaccinations at collecting points. Poliomyelitis, smallpox and BCG vaccines were administered to young children and smallpox vaccine to older children and adults. The smallpox vaccine, until 1970 a liquid vaccine, was produced at the State Vaccine Institute in Cape Town. Vaccination was also given to all children at school entry, and to the 100 000 or

so men who came each year to work in the mines. From 1968 to 1975, between 600 000 and 900 000 persons received smallpox vaccine each year through government facilities. The number of vaccinations was small in proportion to the population, but the total did not include those, said to be many, that were provided by private physicians.

Reporting from the more than 10 000 health units which regularly saw patients was thought to be reasonably good, but because smallpox in South Africa was so mild, the government authorities believed that many persons with smallpox did not seek medical attention and so did not come to the attention of the health services. Teachers and heads of families were also supposed to report cases when they occurred but their level of compliance was uncertain, especially in areas in which religious sects objected to vaccination of any type.

Information about smallpox was very incomplete for other reasons. Responsibility for health problems, as well as the investigation and control of outbreaks of smallpox and other diseases, was regarded as a provincial responsibility, and in the provinces, as mentioned above, this function was primarily discharged by local medical officers of health. Diligence in the investigation of cases and the conscientiousness with which notifications were forwarded varied from area to area. Since the mild variola minor caused the provincial health authorities little concern, not much time was devoted to the investigation or control of outbreaks. The problem was compounded by a national morbidity reporting system considered to be so unsatisfactory that in 1970 a complete

Table 20.10. South Africa: number of reported cases of smallpox, by province, 1960–1972

Year	Cape	Orange Free State	Natal	Transvaal	Total
1960	15	12	0	38	65
1961	0	1	0	7	8
1962	0	0	1	102	103
1963	0	1	35	218	254
1964	54	1	54	193	302
1965	0	0	16	175	191
1966	0	0	14	242	256
1967	0	0	0	43	43
1968	0	0	0	81	81
1969	0	15	26	205	246
1970	0	0	0	121	121
1971	0	0	0	10	10
1972	0	0	0	1[a]	1[a]

[a] Case imported from Botswana.

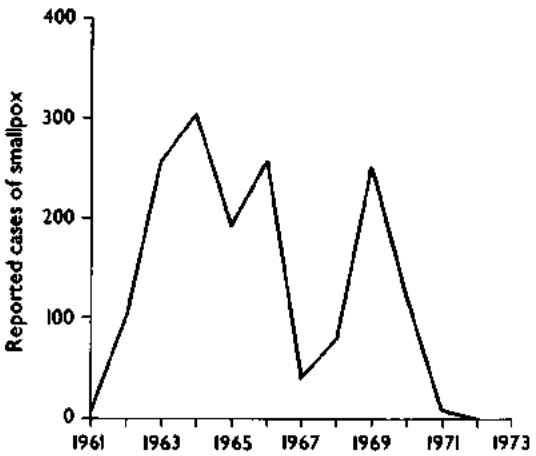


Fig. 20.6. South Africa: number of reported cases of smallpox, by year, 1961–1973.

restructuring of the system was begun. Pending completion of this effort, national morbidity reports ceased to be published in March 1970. Until 1978, further data regarding cases and their geographical location, as notified nationally, were not made available to WHO. When reviewed by WHO in 1978, reports revealed that the Transvaal accounted for most of the cases after 1960 and for all but 41 of the 502 cases reported after 1966 (Table 20.10).

South Africa reported only 43 cases to WHO during 1967, and 81 cases in 1968. Because so few cases were being reported in a country in which health services were so extensive, WHO had originally assumed that these cases must have occurred following importations and had provisionally classified South Africa as a non-endemic country.

In 1969, however, the number of reported cases increased (Fig. 20.6; Table 20.10). Because communication with South Africa through the usual official channels was not possible, Henderson addressed a personal letter to the Secretary for Health on 27 August, noting that as of that date: "South Africa now accounts for about 10% of all cases recorded in Africa this year" and asking for a fuller statement of the epidemiological situation as well as a description of the problems being encountered in controlling spread. By the end of that year, 246 cases had been reported to WHO.

A reply was not received until February 1970. In his letter addressed to Henderson at WHO, the Director of Medical Services showed a dismaying lack of understanding of

the epidemiology of smallpox. He asserted that the cases were sporadic and explained that, with variola minor, "very mild undetected cases and subclinical cases, harbouring the virus in their tonsils, the lymph follicles of the tongue and pharynx are liable to spread the disease to every person not vaccinated against smallpox. Due to this mode of spread, a population with a successful vaccination rate of more than 80% is not protected." He indicated that mass vaccination would continue in order to limit the spread of disease. In reply, Henderson pointed out that in Brazil, in which variola minor was also endemic, "smallpox is transmitted only by cases with definite lesions of smallpox and during the period ... of rash ... and that 80–90% of cases can be traced to personal contact in a house." The favourable experience of other countries in investigating and containing each outbreak was noted and procedures for outbreak containment were described. What effect this correspondence had is unknown.

As it was later learned, the most important stimulus which precipitated a more vigorous programme in South Africa was the WHO Director-General's report on smallpox eradication, prepared as a document (EB45/16; dated 1 December 1969 but never published in WHO's Official Records) for the forty-fifth session of the Executive Board in January 1970 and obtained by South Africa. The report stated:

"Of the endemic countries in Africa, South Africa and Ethiopia are the only ones which have not yet initiated eradication programmes. The number of cases recorded this year by South Africa more than doubled [246 cases in 1969 compared with 81 cases in 1968] ... However, little additional information is available ... The continuing reservoir of smallpox in South Africa and Ethiopia is of increasing concern to neighbouring countries, most of which have become, or are rapidly becoming, smallpox free ... With only three known exceptions, freeze-dried vaccine of satisfactory potency, stability and purity is now used in all endemic countries. However, in South Africa, liquid vaccine continues to be employed..."

South African health officials were angered by the report, considering it to be unfair for three reasons. The first was that the report and the tables of data referred to smallpox only generically, drawing no distinction between the severe variola major of Asia or many other countries of Africa and the mild form of variola minor present in South Africa. This, however, had been a policy followed by WHO since the inception of the programme because the mandate of the World Health Assembly was the eradication of smallpox of whatever variety. The second was the issue of whether or not South Africa could be said to have an eradication programme. As the health authorities viewed it, an effective vaccination campaign was being conducted throughout the country and local authorities were expected to control outbreaks when these occurred. In WHO's view, however, an eradication programme had as its objective the complete interruption of smallpox transmission, an unrealistic aim as seen by the South African Director of Medical Services. The third reason was the emphasis on the use of freeze-dried vaccine—clearly of importance in tropical countries in which ambient temperatures were high and refrigerated storage was scarce. In South Africa, however, ambient temperatures were not so high and refrigerated storage for vaccine was not considered a problem. WHO's emphasis on the need for freeze-dried vaccine in endemic areas was based on the recognition that even when refrigerated storage was adequate, health and medical personnel, even in industrialized countries, often failed to preserve vaccines properly.

Although highly sceptical that other African countries were making as much progress as was claimed, the South African health authorities decided early in 1970 to take additional measures to control smallpox and, by so doing, avoid the expected criticism of other independent African countries. A special programme was launched to produce large quantities of freeze-dried vaccine; by May, all mobile vaccination teams were using this. The vaccine was said to meet WHO standards although it was not examined by a WHO reference laboratory. By the end of 1970, liquid vaccine was being provided only to private practitioners.

In June 1970, an intensified systematic vaccination campaign was begun in the northern Transvaal, from which most smallpox cases were reported. It was termed a house-to-house campaign although, for convenience and efficiency, vaccinators usually assembled persons from a group of neighbouring houses. By the end of the year, more than 350 000 persons had been vaccinated. This represented only a small proportion of the 6.3 million people then resident in the province, although coverage in

the infected but sparsely populated northern areas was said to be high.

By the end of June 1970, 117 cases had been reported to WHO, but thereafter none was notified until December (4 cases) and again in January 1971 (7 cases). As was learned only much later by WHO, all were in the Transvaal, not far from the border with Botswana (Fig. 20.7). Reports from South Africa then ceased. Repeated inquiries were made by WHO officials and others in South Africa after January 1971, under the provisions of the International Health Regulations, asking for confirmation that no further cases had occurred, but there was no response. It was unclear whether there were indeed no cases or whether the government had decided not to report any more cases of smallpox to WHO.

In June 1971, Botswana reported a case of smallpox in Gaborone, the capital, but 2 weeks later asserted that the case had actually been chickenpox. In August, additional cases were reported and these were confirmed as smallpox by laboratory examination. The information was promptly relayed to South Africa and Southern Rhodesia, and teams from both countries immediately went to border areas to conduct intensive vaccination campaigns. The Botswana outbreak continued but only 1 case is known to have been reimported into South Africa—in a labourer who became ill on 14 February 1972.

The question of concern in the autumn of 1971 was how and where smallpox transmission was being sustained in the South Africa–Botswana area. As has been noted, South Africa had reported 11 cases during the 2-month period, December 1970 to January 1971, after 5 months during which no cases had been notified. Following this, 7 months had elapsed before cases were confirmed in Botswana. It was certain that many additional cases had occurred during these two intervals in order to sustain the chain of transmission. Discovery of the infected area was important. Botswana, whose surveillance system was poor, was a candidate area but, because of the letter from South Africa's Secretary for Health, the programme in the latter country had to be regarded with suspicion. WHO Headquarters staff believed it imperative that a visit should be made to South Africa, as well as to Angola and Mozambique, to assess the situation. This was proposed on the grounds that such contact with South Africa was permissible under the terms of a resolution adopted by the WHO Executive Board

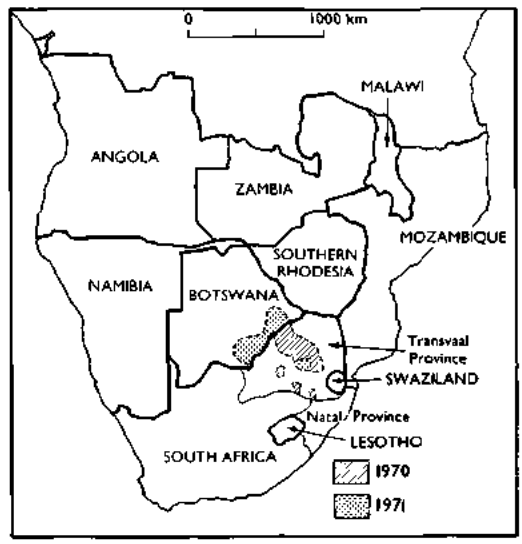


Fig. 20.7. Southern Africa: areas known to have had endemic smallpox, 1970–1971.

(EB45.R20), endorsed by the Twenty-third World Health Assembly in resolution WHA23.46, which had requested the Director-General "to continue to take all necessary steps to assure the maximum co-ordination of national and international efforts". This, it was felt, implied licence to visit South Africa. The proposal was discussed at length and eventually agreement was reached between WHO and the South African government that Henderson should visit South Africa, which he did in June 1972.

In the Transvaal, he found a well-organized vaccination campaign in progress, with attention being given to the detection and laboratory confirmation of suspected cases. During 1972, only a single importation from Botswana had been detected, but health officials were alert because they believed there would be more—if not from Botswana, perhaps from Angola or Mozambique, which they believed continued to harbour endemic smallpox even though neither reported cases.

However, when Henderson endeavoured to obtain epidemiological data regarding the cases reported in 1971, it became apparent that there had been many more cases of smallpox than had been reported to the national authorities. Official records at that time showed only the 7 cases which had occurred in January 1971, in a hospital some 300 kilometres from the border with Botswana. On the other hand, a review of records

at the National Institute for Virology, Sandringham—the diagnostic reference centre—showed 10 poxvirus isolations during 1971, the last from a patient who became ill on 3 May 1971.

The laboratory itself, well equipped and well staffed, was in part inadvertently responsible for problems in smallpox control. It employed an unorthodox approach to the examination of specimens. Standard virological technique called for the isolation of virus on the membrane of fertile hens' eggs. By visual examination of the pocks that grew, variola virus could readily be distinguished from vaccinia virus. At the Institute, the specimens were grown in tissue culture in which, if virus growth occurred, it was impossible to discriminate with certainty between variola virus and vaccinia virus. Accordingly, the laboratory reported only whether or not a virus of the "vaccinia–variola virus group" had been isolated. The laboratory director's view was that whoever sent the specimen should be able to make a clinical distinction between smallpox and disseminated vaccinia, and thus he saw no need to differentiate the viruses by laboratory study. Recipients of the reports, however, sometimes misinterpreted them and reclassified cases of smallpox as vaccinia.

Cases and outbreaks were notified to the regional medical directors by local health officials, who controlled any outbreaks that were found with varying levels of diligence. At neither the national nor the provincial level was there a health official responsible for ensuring that the outbreaks were properly investigated and contained. In no instance had an effort been made to trace the spread of smallpox or to define endemic areas. Reports of variola virus isolations by the reference laboratory were made known only to the persons submitting the specimens; provincial officials were not provided with copies of the reports.

Following Henderson's visit in June 1972, health officials endeavoured to reconstruct the epidemiological pattern of spread of smallpox during 1971. This was important, for if it could be shown that the cases had been closely related and the outbreaks contained, there would be greater assurance that South Africa by 1972 was indeed free of smallpox. Conversely, if the cases had been scattered and unrelated to each other, widespread and perhaps continuing endemicity was implied.

The investigations eventually revealed that smallpox had indeed persisted in South Africa until at least May 1971, all the cases occurring after February having acquired the infection at a hospital about 100 kilometres north of Pretoria, in the Transvaal. As far as the outbreak could be reconstructed, 3 unvaccinated children from a village 30 kilometres distant were hospitalized with typical smallpox in January and February 1971 and the diagnosis was confirmed by virus isolation. The mother reported that her other 4 children, as well as a number of children in the vicinity, had been ill with a similar disease. Three additional children from the same village were admitted with smallpox during January and February, although no specimens were collected. On 26 March, a child hospitalized with tuberculous meningitis and receiving steroid therapy developed a rash at first thought to be drug-induced. Specimens were taken and the National Institute for Virology reported the isolation of a virus of the vaccinia–variola group. The report was misinterpreted and it was concluded that the child had experienced disseminated vaccinia. The patient died on 3 April. Three additional cases occurred in previously hospitalized children on 12, 14 and 19 April respectively, all of which were confirmed by virus isolation. The Regional Medical Director, who was asked to investigate, reported as follows:

> "The suspected outbreak has occurred in the TB ward. One death [not officially notified] is attributed to the disease which had been diagnosed also in 3 other children who were examined. In addition, 3 cases of healing chickenpox were examined. According to my information, the latter disease has been "endemic" amongst children in this ward for many months. That is to say chickenpox has been diagnosed also amongst other children who have no visible lesions now and also in children who have been discharged already ... Vaccination of patients and personnel ... carried out 7 April did not give a satisfactory percentage of takes ... The ward was placed in quarantine only this week. Therefore, a list was compiled of all inmates and also of all patients discharged ... The homes of all will be visited by departmental field staff."

A large hospital-based outbreak of smallpox and possibly of chickenpox had obviously been in progress for at least 2 months. Extensive vaccination campaigns were conducted subsequently in the many

areas from which the hospital patients had come. Three additional cases were found, all of whom had been infected at the hospital: a child who had been hospitalized became ill on 3 May, and 2 labourers who had been seen in the outpatient department 2 weeks earlier became ill in March on a farm 100 kilometres distant. In all, 10 cases and 1 death appear on the official records for 1971 but, as is apparent from this account, there were at least 20 cases and possibly many more. Fortunately, the outbreak occurred at the end of the summer, the low point in seasonal transmission, so that despite greatly delayed containment measures, smallpox spread slowly and transmission was soon interrupted.

In South Africa, as in other countries of southern Africa, extensive vaccination rather than an organized surveillance–containment programme served to interrupt transmission. During the continuing vaccination campaign, no further cases were detected and none was reported by the 11 000 reporting units. Among 77 specimens submitted to the laboratory over the period 1972–1977, only 1 further isolation of the "vaccinia–variola group of viruses" was made, the specimen concerned being from the case (see above) that was imported from Botswana in 1972.

Botswana

Botswana, which became independent in 1966, is large but sparsely populated, the great Kalahari desert extending over the south-west portion of the country and occupying more than half the land area. Over 80% of its population of 623 000 (1970) lived along a strip of land in the south-east, not more than 200 kilometres wide, adjacent to the Transvaal Province of South Africa. Travel between Botswana and South Africa was frequent; population movement within the country was extensive and followed an unusual pattern. A large proportion of the population maintained 3 dwellings: one in a village, a second at a cattle post and a third in a farming area. Family members spent time each year in the different locations, which were often widely separated. Moreover, an estimated one-third of the adult males left rural areas each year seeking employment in the country's urban areas or in South Africa. Government health facilities were comparatively numerous; in 1966 there were 7 hospitals, 73 clinics and 65 health posts.

Table 20.11. Botswana: number of reported cases of smallpox, 1959–1974

Year	Number of cases
1959	5
1960	31
1961	36
1962	8
1963	2
1964	175
1965	0
1966	0
1967	1
1968	0
1969	0
1970	0
1971	36
1972	1 059
1973	27
1974	0

Several missionary groups also provided medical care.

In this small and scattered but highly mobile population, smallpox was characterized by periodic outbreaks followed by long intervals with few or no cases. An outbreak of 175 reported cases and 34 deaths in 1964 was controlled by a mass vaccination campaign and during the following 6 years only 1 case was notified (Table 20.11).

Because Botswana was believed to be smallpox-free when the Intensified Smallpox Eradication Programme began and because adjacent countries were reporting few or no cases, the development of a special programme was not considered by WHO to be of high priority—if it was required at all. As time passed, the apparent need for a programme diminished. Neighbouring Namibia and Angola reported no cases and Zambia became smallpox-free in 1968. The only other

Table 20.12. Botswana: number of smallpox vaccinations performed, 1965–1977

Year	Number of vaccinations
1965	..[a]
1966	47 697
1967	48 807
1968	39 253
1969	19 582
1970	46 000
1971	112 000
1972	402 000
1973	149 000
1974	68 876
1975	93 345
1976	62 235
1977	95 660

[a] .. = data not recorded.

adjacent countries notifying cases, South Africa and Southern Rhodesia, reported so few in 1967–1968 that WHO suspected that they were the result of importations rather than of endemic transmission. By the end of 1969, however, the number of reported cases in South Africa had increased so greatly that it seemed certain that endemic smallpox was present there. Although the government informed WHO that some of the cases were in Transvaal Province, their exact whereabouts were not revealed. Only in 1972 did it become known that virtually all the reported cases had occurred in the Transvaal, many near the border with Botswana.

Ladnyi paid his first visit to Botswana in January 1971 to discuss the status of its vaccination campaign and the assistance that WHO might be able to offer. After Botswana's mass vaccination campaign of 1964, some vaccination activities had continued (Table 20.12). Liquid vaccine from South Africa had been employed up to the end of 1969, and thereafter freeze-dried smallpox vaccine, also purchased from South Africa, was used. Vaccinations were given by mobile teams in 3 of the 6 health districts and offered by hospitals and clinics throughout the country. However, the health facilities for the most part vaccinated persons leaving for South Africa and Zambia, both of which countries required certificates of vaccination. The number vaccinated each year was equivalent to no more than 5–10% of the population. The proportion of successful vaccinations is unknown but was probably not high even when freeze-dried vaccine began to be used. The freeze-dried vaccine was provided in 100-dose containers and was normally used for 1–2 weeks after reconstitution, although its potency would have fallen to nil within 2–3 days.

Ladnyi found that 80% of the pre-school children had no vaccination scar, and in a school near the capital whose pupils had recently been vaccinated by a mobile team, only 136 of 334 children (41%) had a vaccination scar. Better handling of the vaccine was obviously needed and he provided appropriate advice.

Ladnyi was concerned that smallpox might be imported, and his principal recommendation was that every suspected case of smallpox should be treated as an emergency and all necessary containment measures carried out with a minimum of delay. He recommended that a specimen should be taken from each suspected case and sent to WHO Headquarters for examination; meanwhile the suspected case should be dealt with as though it were smallpox. In a country in which vaccinial immunity was so low, there was a special need for prompt action. The government requested vehicles and vaccine in support of the programme, a request which was forwarded to the WHO Regional Office for Africa.

On 1 June 1971, only 5 months after Ladnyi's visit, a cable was received in Geneva from Botswana reporting a case of smallpox. At that time, no cases had been reported from anywhere in southern Africa since January, although it was learned later that cases in South Africa continued to occur through May. Cables sent on 4 and 8 June from Botswana indicated that the case was in a patient already hospitalized in Gaborone, and that it had been confirmed virologically at South Africa's National Institute for Virology.

Urgent action was indicated. However, permission for WHO Headquarters staff to visit a country required the prior agreement both of the WHO regional office concerned and of the country itself. Henderson immediately telephoned the regional office in Brazzaville to point out the urgency of rapid containment and of a thorough investigation and to propose that an experienced epidemiologist from Headquarters should visit Botswana immediately. The regional office contacted Botswana and, on 16 June, reported that a cable had been received from the government indicating that the situation was misunderstood, that the case had turned out to be chickenpox, and that no visit was required. A return telex from Geneva to Brazzaville again urged an early visit by a WHO adviser in view of the fact that the case was said to have been confirmed by laboratory investigation. The regional office replied that such a visit was not considered advisable.

On 27 August, additional cases of smallpox were reported from Botswana, and specimens were sent by the government direct to Geneva. By 6 September, the WHO Regional Reference Centre for Smallpox in Atlanta, USA, had confirmed the isolation of smallpox virus. This caused a flurry of telex messages and letters between Geneva and Brazzaville. Headquarters staff repeatedly urged an emergency visit by Arita, pointing out that the Botswana focus presented a continuing threat to Botswana as well as neighbouring coun-

tries and noting that this was clearly as much an international as a national problem. The regional office requested more information from Botswana and asked whether WHO assistance was required.

On 7 September 1971, a letter was received in Geneva addressed to the Chief of the Smallpox Eradication unit from the Director of Medical Services of Botswana. Contrary to the cabled information received by the regional office, he reported that in May a 3-year-old child, hospitalized for tuberculosis, had developed smallpox and that a second case had been detected in a government employee in Gaborone on 16 August. Specimens from both had been confirmed as "vaccinia–variola type virus" by the South African National Institute for Virology. The second case had been vaccinated during a June vaccination campaign in Gaborone but showed no scar. The Director of Medical Services noted that "... no source of infection has been identified. There must, however, be a focus of infection somewhere".

On 20 September, Botswana requested a supply of freeze-dried vaccine—which was immediately sent from Geneva—and an operations officer to organize a vaccination campaign. However, as a new intercountry smallpox adviser, Dr Islam, had just replaced Ladnyi, whose current term of service in WHO had expired, he was sent instead. Unfortunately, despite his experience in the control of communicable diseases, he had not yet had direct experience with smallpox eradication and had not yet been briefed regarding techniques for surveillance and containment.

He arrived for a 15-day visit on 8 October by which time 3 additional smallpox cases had been detected and a fourth suspected case had been admitted to hospital. He was unable to trace the sources of these cases. The cases he did identify were in people who presented themselves at the hospital, and he indicated that "there is strong evidence that a smallpox focus exists ... in the southern part of Central District ... the investigations do not support the notion of recent importation". A mass vaccination campaign was said to have been conducted but, in fact, only 38 600 vaccinations had been recorded between January and August 1971. In the area of the smallpox focus, he found that 80% of 1767 primary-school children and 60% of 541 pre-school children had vaccination scars. In adjacent areas, however, only 20% of those aged 0–6 years had ever been vaccinated. He recommended a mass vaccination campaign in the primarily infected area, offered advice to the government regarding vaccine handling and vaccination technique and stressed the importance of surveillance. At this time, these were the only known cases of smallpox in the entire WHO African Region, the other countries in the African continent in which the disease was still endemic, Ethiopia and the Sudan, both then being in WHO's Eastern Mediterranean Region.

Cases continued to be reported from Botswana and all specimens sent for examination to the WHO collaborating centres were confirmed as smallpox, but no information was provided by the government as to what was being done to control the spread of the disease. Faced by frequent and increasingly urgent requests from WHO Headquarters to respond to Botswana's request for an operations officer, the regional office could only reply that no action could be taken unless it received an official application from the government.

In November 1971, an unexpected opportunity arose that permitted direct communication with Botswana. Mr John Phillips, the Resident Representative of the United Nations Development Programme in Botswana, stopped in Geneva on the way back to his duty station. After a full discussion of the problem with WHO staff, it was agreed that he would discuss it with government officials and ask them to submit a formal request to the regional office for the immediate assignment of an operations officer. The request was made forthwith, and Dr Pierre Ziegler, in charge of smallpox eradication in Zaire, was asked to make available his most experienced operations officer, Mr Garry Presthus (see Chapter 18, Plate 18.5). His transfer was not, however, arranged until the end of February 1972, nearly 9 months after Botswana had notified its first case.

On arrival, Mr Presthus, with his counterpart, Mr J. B. Sibiya, Senior Health Inspector for Botswana, rapidly set in motion a mass vaccination campaign and a programme which, unique among the programmes of southern Africa, emphasized the prompt detection of cases and their containment through vaccination. More than 18 months would elapse, however, before transmission could be interrupted.

Within a month of his arrival, Mr Presthus had met the director of the Botswana Red

Plate 20.3. **A:** Joseph B. Sibiya (*far left*), Senior Health Inspector, with one of Botswana's 4 surveillance teams. **B:** Many cases of smallpox were discovered in remote cattle posts in the Kalahari desert by the teams.

Cross, Ruth Seretse Khama, to explain the importance of smallpox eradication in Botswana and its significance for the global programme. In mid-April 1972, her husband, Sir Seretse Khama, the President of Botswana, had signed a special bill allocating US$25 000 from the government budget. Although not a large sum in comparison with funds provided in some other eradication programmes, this represented a substantial commitment for Botswana.

Using such vehicles as could be borrowed from other programmes, Mr Presthus and Mr Sibiya formed 4 teams to contain outbreaks in known foci and to encourage the network of health facilities to begin vaccinating both

people attending clinics and the inhabitants of nearby villages (Presthus, 1974). By early May 1972, forms had been prepared to be used for weekly reports from each health unit. Volunteers of all types offered assistance.

Field investigations conducted during March documented 36 cases which had occurred during 1971, the first in March near the South African border. Mr Presthus believed that there had been many more cases, but with new cases being detected daily there was no time to document further the previous year's experience.

In 1972, the number of reported cases increased to 63 in April and to 66 in May (Table 20.13). In that month, one of the cases was reported from Ngamiland, in the northwestern part of the country, an area of great concern because of the frequent movement of rebel forces between it and areas in southeastern Angola which were only partially accessible to the government of Angola. A surveillance team was hurriedly sent to the area, but fortunately there was an able District Medical Officer, in Ngamiland, Dr Nicholas Ward, who had already organized the health staff for extensive vaccination and search activities. Only 5 other cases were eventually detected in Ngamiland. A year later Dr Ward was recruited by WHO, which he served with distinction in smallpox eradication work in Bangladesh and India.

The increase in the number of cases in April and May 1972 was of profound concern. Although little was known of past seasonal trends of smallpox in Botswana itself, it was assumed that more rapid transmission would occur during the cooler months of the year, from June to the end of October. Accordingly, at the end of May, the WHO intercountry smallpox adviser was directed to assist Mr Presthus and Mr Sibiya in surveillance–containment operations.

Hospital and clinic staff meanwhile had responded enthusiastically to the request that they should vaccinate people in nearby villages, and by the end of July more than

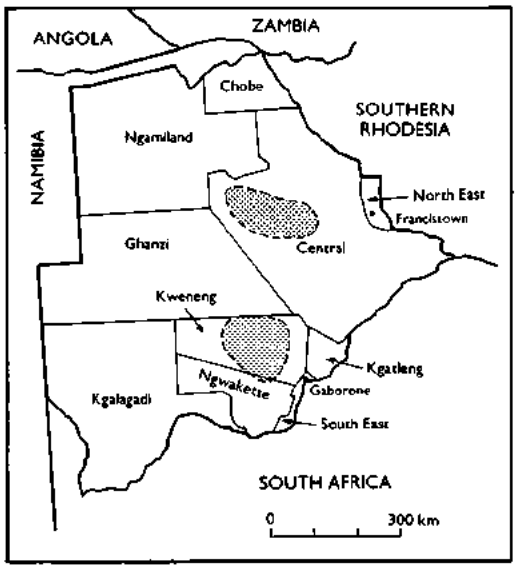


Fig. 20.8. Botswana: areas affected by smallpox, by district, at the end of July 1972.

200 000 had been vaccinated—5 times as many as were customarily vaccinated in an entire year. Meanwhile, the 3 surveillance teams sought to detect and contain outbreaks. The investigation of 48 hospitalized cases revealed 321 others. Because many were being traced to Kweneng District (Fig. 20.8), a systematic search was conducted throughout this area, revealing another 355 cases. Virtually all the cases were detected at cattle posts in rural areas, far distant from the clinics and health posts. Meantime, a second but less seriously affected area was found in Central District.

The number of cases detected increased to 121 in June and to 565 in July. Most were in Kweneng and Central Districts (Table 20.14). Analysis of 39 outbreaks comprising 353 cases revealed an average of 9 cases in each outbreak with a range of 3–30 cases; one-fourth of the outbreaks had persisted for 4 or more genera-

Table 20.13. Botswana: number of reported cases of smallpox, by month, 1971–1974

Year	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
1971[a]	0	0	(1)	0	(2)	1	(2)	2	4	6	8	10	36
1972	1	4	20	63	66	121	565	133	33	52	1	0	1 059
1973[a]	(2)	(3)	(7)	(4)	0	(1)	(1)	(2)	(1)	(1)	(5)	0	27
1974	0	0	0	0	0	0	0	0	0	0	0	0	0

[a] ( ) = Cases shown by month of onset. Most of these cases were not discovered until many months later.

Table 20.14. Botswana: number of reported cases of smallpox, population by district, and number of vaccinations performed, 1971–1973

District	Estimated population[a] (1973)	1971	1972	1973
Central	234 828	31	84	15
Kweneng	72 093	0	954	0
Ngamiland	53 870	0	6	0
Ngwaketse	91 310	0	6	0
South East	54 047	5	9	12
Other	124 231	0	0	0
Total	630 379	36	1 059	27
Number of vaccinations (thousands)		112	402	149

[a] Population estimates as recorded in 1973. United Nations (1985) data show a total population of 698 000 for Botswana as a whole in 1973.

tions of disease. The interruption of transmission was difficult, however, because the mildness of the disease permitted infected persons to travel between their different residences, which they did frequently.

Lack of vehicles hampered the work of the smallpox eradication teams. Four Land Rovers had been ordered in February but, despite efforts to speed their delivery, they did not arrive until November 1972. Nevertheless, the teams organized by Mr Sibiya and Mr Presthus worked tirelessly, and by the end of the year 402 000 persons had been vaccinated. From July onwards, 83% of the 19 designated reporting units sent in weekly reports, although some of these were not received until 1 or 2 months after dispatch because of the poor postal service. Accordingly, health staff throughout the country were instructed to use the telephone or telegraph if a case was found. However, an analysis of reports at the end of November showed that only 5% of cases were seen by the health care units, the remainder being detected by outbreak investigation and active search.

Although it was the season of high transmission, the numbers of cases decreased sharply after July. Meanwhile, in response to warnings about the problem in Botswana, South Africa and Southern Rhodesia undertook extensive vaccination campaigns throughout their border regions, and in Angola, military forces were employed in vaccinating the inhabitants of large areas in the south-east. They detected no cases.

Although resources available to the programme were limited and the population was widely scattered, relatively high levels of vaccinial immunity were achieved in less than a year (Table 20.15).

The search for cases continued after November 1972 but none was found until March 1973. On 7 March, a 22-year-old man was admitted to the hospital in Gaborone with suspected chickenpox, which proved to be smallpox. A house-by-house search began in the vicinity of the patient's home; it was extended to Gaborone and, finally, to a cattle post, 40 kilometres away, in which the patient had spent a night. No other cases could be found until, after 3 weeks of search, a schoolchild identified a person who had recovered from smallpox and was being hidden from the teams. The patient was a member of a Christian sect, known as the Mazezuru, which opposed medical treatment and resisted vaccination.

The search was then focused on Mazezuru families, and 19 cases were eventually identified, the first having been infected in late September 1972 in Kweneng District in an area in which the last cases had been detected that year. Two slowly spreading chains of infection had developed: one chain consisted of 9 cases in Gaborone, of whom all but the hospitalized patient were Mazezuru; and one chain of 10 cases in a town 400 kilometres to the north, in which 4 Mazezuru had been infected. The last of the cases occurred on 13 April 1973.

Table 20.15. Botswana: results of vaccination scar surveys, by age group and district, January–March, 1973

District	0–5 years		6–14 years		⩾15 years	
	Number examined	% with scar	Number examined	% with scar	Number examined	% with scar
Central	2 731	77	17 748	86	8 370	86
Kweneng	1 599	80	6 118	84	3 669	88
Ngamiland	178	82	1 167	86	722	86
South East	800	78	3 204	79	1 479	77
Other	3 021	71	9 525	79	7 734	68

G I PRESTHUS

Plate 20.4. The child in this Mazezuru family developed smallpox on 7 November 1973; another patient with the same source of infection, who became ill on 15 November, was the last known case in Botswana.

Active search continued, with special attention to the Mazezuru. This sect was estimated to comprise only 3500–5000 persons, who lived in 9 closed or semi-closed communities in towns near the railway. They were traders who travelled frequently to visit relatives and friends in South Africa and Southern Rhodesia as well as in other areas of Botswana. Fortunately, they were distinctive in that the women wore all-white clothing and the men were frequently bearded. So strongly did they object to vaccination that on one occasion in April a community of 100 persons left by train when they learned that a team was coming to vaccinate them. Extensive discussions with Mazezuru church leaders led to a verbal agreement that they would persuade their people to accept vaccination. Later, it was learned that the leaders had privately advised the members of their sect to refuse to cooperate.

From April to September, no cases were detected, but in September another case appeared at a hospital; the patient was a non-Mazezuru girl who lived in the Mazezuru quarter of a migrant settlement near a mining complex. Five weeks of intensive search turned up 5 more cases, but from discussions with people living in the area, it was suspected that at least 6–10 additional cases had occurred. The first patient had become ill in June and the last on 14 September. Again, nearly 2 months elapsed, when, on 21 November, yet another case was found in the mining camp, and this in turn led to 2 more cases at the camp and 3 cases in Gaborone, the last of whom had become ill on 15 November.

More stringent measures were required to interrupt the tenuous but tenacious chain of transmission among the Mazezuru. Most Mazezuru were comparatively recent immigrants to Botswana, having come mainly from Southern Rhodesia. To enter South Africa or Southern Rhodesia they were obliged to be vaccinated and they accepted this as a necessity. Mandatory vaccination in Botswana was proposed to the President of the country. He concurred and informed Mazezuru leaders that either their co-religionists must accept vaccination or they would be deported. They agreed to be vaccinated.

From 1974 onwards, both smallpox and BCG vaccinations were administered by the health facilities in substantial numbers, scar surveys in 1974 revealing an overall level of vaccinial immunity of 95%. The 4 surveillance teams continued to encourage and supervise this activity and to search for cases. Many suspected cases were investigated and specimens examined but none proved to be smallpox.

Information regarding the age and vaccination status of cases is shown in Table 20.16. Nearly half the cases occurred in individuals aged between 5 and 14 years. The occurrence of 34% of cases among adults is

Table 20.16. Botswana: number of reported cases of and deaths from smallpox, by age group and vaccination status, 1971–1972[a]

Age group (years)	Number of cases (%)	Number with vaccination scar	Number of deaths
<1	17 (2)	0	1
1–4	195 (18)	3	1
5–14	505 (47)	11	0
≥15	365 (34)	18	0
Total	1 082	32	2

[a] Further details not available for 13 other cases reported during this period.

high compared to the situation in most countries, but it is not unexpected considering the low level of vaccinial immunity in Botswana. Cases in infants (0–12 months) were thought to have been underenumerated because of the tendency of parents to hide young children with smallpox. Thirty-two of the cases (3%) were reported to have had a vaccination scar, but some of these were individuals vaccinated late in the incubation period. Only 2 deaths are known to have occurred (a reflection of the mildness of the disease); one of them was the child with tuberculosis, already mentioned, who was receiving steroid therapy and the other was a 2-week-old infant.

ANGOLA

Angola (population in 1970, 5.6 million) reported no case of smallpox after 1966. It had an extensive network of hospitals, health centres and rural dispensaries which offered smallpox vaccination. In addition, 300 "rural agents" travelled through assigned areas of the countryside giving vaccinations. Separate mobile units, numbering 26 in all, dealt with leprosy, trypanosomiasis and tuberculosis; they also administered smallpox vaccine. Freeze-dried vaccine obtained from Portugal, France or Switzerland had been used since the mid-1960s. Because freeze-dried vaccine was in use and the number vaccinated annually amounted to 30–60% of the population, vaccinial immunity was probably high. Until 1959, when transmission appears to have been interrupted, variola minor was the prevalent strain: among 1712 cases reported between 1950 and 1959, there were only 23 deaths. Outbreaks due to smallpox imported from Zaire occurred in 1962 (23 cases), 1963 (50 cases), 1964 (1 case) and 1966 (3 cases). Each was investigated by epidemiologists from Luanda, the capital, and confirmed by virus isolation at a laboratory there. The extensive national programme of vaccination continued until the end of 1974, a special campaign being conducted in 1971–1972 in areas adjacent to Botswana; no imported cases were discovered after 1966. Vaccination and surveillance activities were sharply curtailed during 1974–1975, when civil war erupted, but by then more than 2 years had elapsed since the major outbreaks in Botswana and more than 3 years since the last cases had occurred in Zaire.

CONCLUSION

As had been expected in 1967, smallpox in southern Africa was not a major problem, but transmission continued far longer than had been anticipated. Constraints on official communication between WHO and the health authorities in several of the countries or areas unquestionably inhibited progress. In most instances, national health officials were capable of investigating and containing outbreaks, but they needed instruction and assistance to carry out the task in a proper manner. Because the incidence of smallpox was low, effective surveillance and containment might have interrupted transmission much earlier and the final epidemic in Botswana would not have occurred.

Considering the extensive number of health units and special vaccination campaigns in operation throughout southern Africa, it is perhaps surprising that smallpox was not eliminated from this area long before 1967. However, in many of the countries few of the health units offered vaccination, even to people attending their clinics. Moreover, except in Angola and Mozambique, liquid vaccine was the only type of vaccine used, and when supervision was poor, as in Botswana, Malawi and Zambia, the vaccine was not properly refrigerated and there were comparatively few successful takes. When freeze-dried vaccine became widely available, the numbers of cases of smallpox diminished rapidly and transmission was soon interrupted, even though, with the exception of Angola and Botswana, few outbreaks were investigated or contained.

The concluding episode in southern Africa—namely, the reinfection of and extensive spread of smallpox in Botswana—was regrettable and, in retrospect, avoidable. Re-establishment of endemic smallpox might have been averted if a programme in Botswana had been initiated a year or more earlier. That Botswana was at significant risk, however, had not been appreciated. The principal endemic focus of smallpox in South Africa was in the Transvaal, near the border with Botswana, but this was not made known to WHO until after smallpox had become endemic in Botswana. For their part, the South African authorities had been little concerned with the mild variola minor that was present and rarely investigated or contained the outbreaks that did occur. However, even as late as June 1971, when the

first case was reported in Botswana, prompt action might have aborted the ensuing epidemic. Unhappily, there was a delay of fully 9 months before an effective programme began. By then, an intensive and more costly effort was required to stop transmission. Botswana's programme, once begun, was imaginatively and competently executed—the best of any in southern Africa.

The exceptionally mild form of variola minor found in Botswana and South Africa did not constitute a problem of public health significance; had this form of smallpox prevailed throughout the world, a global eradication programme would not have been warranted. It was clear, however, that unless smallpox as a disease, whatever its degree of severity, were eradicated, long-standing programmes of vaccination and the issuing of vaccination certificates for travellers would continue to be required. The eradication of variola minor in Botswana and South Africa was as important to the global programme as was the eradication of variola major.

CHAPTER 21

ETHIOPIA, YEMEN AND DEMOCRATIC YEMEN

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INTRODUCTION

The execution of successful eradication programmes was a challenge to all countries, but for those which in 1967 had only just begun to develop national infrastructures for health, transport and communication it presented a staggering problem. Ethiopia, with a population of 25.5 million (in 1970), was by far the largest and most populous of countries in this category. Across the Red Sea lay the much smaller states of Yemen (population, 4.8 million) and Democratic Yemen, with its sparse population of 1.5 million (Fig. 21.1). The problem was complicated by civil strife, which was present in all 3 countries either at the beginning or during the course of the Intensified Smallpox Eradication Programme.

In 1967, smallpox was considered to be endemic in both Ethiopia and Yemen; Democratic Yemen, which had reported no cases since 1961, was provisionally categorized as smallpox-free. Because health services were sparse and so few persons were routinely vaccinated, it was feared that the incidence of smallpox in Ethiopia and Yemen might be among the highest in the world; also, the smallpox-free status of Democratic Yemen had to be regarded with some scepticism.

Recognizing that effective national eradication programmes would take time to establish, WHO began to explore the possibility of developing such programmes in each of the 3 countries as soon as the Intensified Programme was launched in 1967. Four years elapsed, however, before eradication activities had been established in all 3 countries. Plans for a programme in Yemen had been discussed by government and WHO staff as early as 1959, a plan of operations had been signed in 1961 and some vaccine had been provided. However, a civil war broke out which lasted 5 years, and little could be achieved until 1969, when a revised plan of operations was agreed on and a special smallpox eradication unit created within the Ministry of Health. Democratic Yemen embarked on a programme in 1970 and, finally, in 1971, Ethiopia followed suit—the last of the countries which had endemic smallpox in 1967 to participate in the Intensified Programme.

The programmes were each very different in character and operated independently of

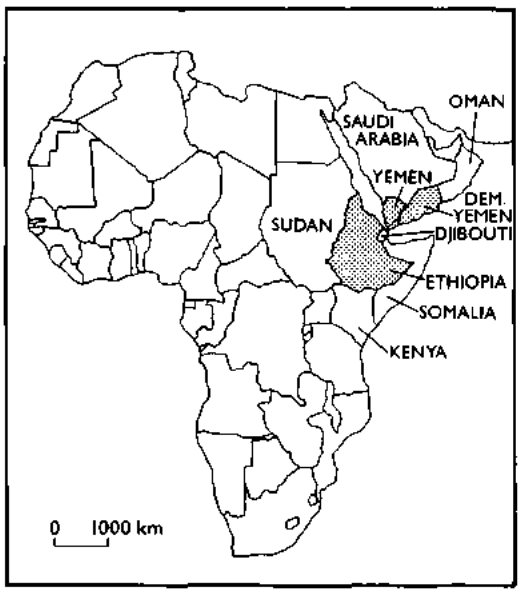

Fig. 21.1. Horn of Africa and adjacent countries.

one another. Epidemiologically, they were also distinct. Despite their geographical proximity, none of the 3 countries is known to have imported cases from either of the others after 1967.

Yemen began a systematic vaccination campaign in 1969 in urban districts and areas accessible by road. After little more than a year, during which 1 million vaccinations were performed, the campaign quickly deteriorated to the point that 5 years elapsed before another million persons were vaccinated. After the programme had begun, only 29 poorly documented cases were recorded in 1969, and none thereafter. From 1971 to 1977, specimens were obtained from 26 suspected cases but none showed evidence of variola virus. Although WHO provisionally reclassified Yemen as a non-endemic country in 1970, this decision was grounded primarily on the absence of reported cases; little other information was available. Because the reporting system was poor and surveillance all but nonexistent, the true status of smallpox remained uncertain until 1978. In that year, a carefully conducted national survey confirmed the absence of smallpox during recent years and suggested that the disease had indeed been absent since 1969.

Between 1970 and 1972, Democratic Yemen conducted an extensive vaccination campaign in and around Aden, the capital city, and in 1973 extended it to other parts of the country. Surprisingly, only 1 case of smallpox was reported, in 1968, but this report was subsequently retracted, it being alleged that the case had been one of misdiagnosed chickenpox.

Ethiopia's participation in smallpox eradication did not begin until 1971, and up to 1975 the government gave it limited support. Two factors were primarily responsible: (1) national and international malaria eradication programme staff had initially opposed undertaking a programme which they believed would adversely affect their own activities; and (2) when the smallpox eradication programme finally began, it was discovered that only the mild variola minor form was present in Ethiopia, and among the many health problems confronting the government, this disease was not of major consequence. During the first 4 years of the programme, fewer than 100 Ethiopian health personnel, WHO staff and international volunteers, travelling mainly on foot and on muleback, struggled desperately to contain widespread and persistent smallpox. The task was made more difficult by the wide dispersal of the population, more than half of whom lived more than a day's walk from any sort of road in extraordinarily rugged terrain; by a rudimentary governmental infrastructure; and by a dearth of health facilities and manpower. Continuing civil war, hostile groups who resisted vaccination, famine and flood further complicated the effort. Yet, surprisingly good progress was made with the limited resources available. However, smallpox persisted stubbornly throughout vast rural areas, in contrast to the situation in Yemen, in which control measures in the few urban areas were quickly succeeded by the interruption of transmission in the country as a whole. Following the eradication of smallpox in Asia in 1975, greater resources could be made available to Ethiopia, and the new revolutionary government gave substantial additional support. An intensified programme with more adequate resources succeeded in interrupting transmission in August 1976.

The 3 national programmes are described in this chapter in chronological order of commencement, beginning with a brief account of activities in Yemen and Democratic Yemen and concluding with a more detailed description of the Ethiopian programme, which was one of the most difficult, complex

and imaginative of any national eradication campaign.

In this chapter, the spelling of Ethiopian geographical names adopted by the Ethiopian Mapping Agency in 1978 has been followed (Tekeste et al., 1984).

YEMEN

Yemen, the most densely populated country in the Arabian Peninsula, is situated on an ancient route used by pilgrims, many of them from Asia and some from Africa. After travelling by sea to the port of Aden, 100 kilometres to the south of Yemen, or to other ports on the Arabian Peninsula, or overland, many pilgrims passed through Yemen on their way to Mecca.

The country has an area of 195 000 square kilometres and consists of 3 different geographical regions. The first is a hot arid semi-desert strip, 30–70 kilometres wide, extending along the shores of the Red Sea and inhabited, in 1967, by perhaps 20% of the population, many of African origin. The second area, inhabited by 75% of the population, is a high plateau, about 100 kilometres wide, with densely populated river valleys and scattered villages among rugged mountains. The third area, in the east of the country, is a sparsely populated arid desert in which, in 1967, not more than 5% of the population lived.

Until 1962, when it became a republic, Yemen had been ruled by feudal tribal leaders and was largely isolated from the outside world. According to the first census, taken in 1975, 5.2 million persons were living in the country, and an estimated 1.2 million were working abroad, mainly in Saudi Arabia. Less than 1000 kilometres of roads connected the 3 main towns, Sana'a (population, 100 000) and Taiz (population, 30 000) in the mountains and Hodeida (population, 50 000) on the coast. Most of the population lived in an estimated 15 000 villages, the majority of which could be reached only on foot or on muleback.

During the rule of the tribal leaders, neither health nor educational facilities had been widely developed and such facilities as did exist were primarily confined to the 3 main towns. When the country became a republic in 1962, efforts were made to introduce a modern form of central government, but they were severely hampered by 5 years of civil war. In 1967, more than 90% of the population was illiterate and few people had access to either curative or preventive health services. As recently as 1978, 70% of the 162 districts in the country had no health facilities whatsoever.

Little is known about smallpox in Yemen, there having been no national reporting system until 1975. However, because of the relative isolation of the population, outbreaks were probably infrequent in much of the country. Data from what had been the Protectorate of South Arabia, which included the port of Aden, now the capital of Democratic Yemen, show few or no cases and very few deaths in recent decades, until 1957, when 65 cases with 19 deaths were recorded. The source of infection was reported to have been Pakistan. Outbreaks continued in the Protectorate between 1957 and 1961, and smallpox may well have spread from Aden to Yemen, in which an epidemic started in 1957 or 1958 and continued for several years. It was said to have resulted in not less than 30 000 cases and 18 000 deaths. Assistance from WHO was requested and a team was sent to investigate in June 1959. The team found no active cases in Sana'a, the capital city, but noted large numbers of persons with facial pockmarks. A report from a village of 800 inhabitants stating that only 200 of them had survived the epidemic was indicative of its severity. The evidence, such as it is, suggests that a severe epidemic of variola major had occurred among a population which had experienced little smallpox in recent decades.

During succeeding years, some vaccine was provided by WHO and through bilateral assistance. Vaccination was made available in hospitals in the 3 major towns and at the 20 or so health centres when outbreaks occurred. However, not more than 15 000 or 20 000 individuals were vaccinated each year. In 1962, with assistance from WHO, a national vaccination campaign commenced. Forty vaccinators were recruited and trained; the population of Sana'a was vaccinated in a house-to-house campaign, but thereafter these activities diminished with the gradual intensification of civil strife. Reports obtained during the certification procedure in 1978 suggest that the epidemic of variola major subsided in 1963. WHO was officially notified by Yemen of the occurrence of 5 cases of smallpox in 1964, of 1 case in 1966 and of 3 in 1967, but nothing more is known of these cases or where exactly they occurred.

Reporting at that time was not good and WHO did not endeavour to elicit more complete information about cases until the Intensified Programme was well under way.

In 1967, Yemen was provisionally classified by WHO as an endemic country with the expectation that an effective surveillance programme would probably reveal many hundreds, if not thousands, of cases. Because one of the principal routes of the Mecca Pilgrimage passed through it, Yemen constituted a potential focus for the spread of smallpox to Africa and other countries of Asia. The early initiation of an eradication programme was therefore thought to be vitally important. However, a *coup d'état* in 1967 and continued fighting between republican and royalist forces delayed the start of the work.

In 1968, discussions with government officials led to the approval of a plan of operations for a WHO-supported programme, to begin in July 1969. WHO agreed to provide a medical officer, vaccine, vehicles and a per diem allowance for national staff travelling in the field. In the course of the following decade WHO provided some US$313 000 in support of the programme (about US$0.06 per head of population), as well as 3 million doses of vaccine (Table 21.1). The government agreed to provide a counterpart medical officer, 53 vaccinators and 20 auxiliary staff for a 3-year national vaccination campaign during which it was planned to vaccinate 4 million persons (Table 21.2). The development of surveillance was considered an essential component of the plan although it received little attention from the programme staff.

Table 21.1. Yemen: WHO support provided to the smallpox eradication programme, 1967–1979

Year	Personnel, supplies and equipment (US$)	Doses of vaccine (thousands)
1967	-	250
1968	15 424	-
1969	47 219	315
1970	41 864	245
1971	22 999	735
1972	11 184	210
1973	39 064	245
1974	11 713	145
1975	25 148	450
1976	11 215	-
1977	11 986	252
1978	45 483	100
1979	29 814	64
Total	313 113	3011

Table 21.2. Yemen: number of vaccinations performed and number of reported cases of smallpox, 1967–1975

Year	Number of vaccinations performed	Number of vaccinations planned[a]	Number of cases reported
1967	141 200	-	3
1968	46 000	-	0
1969	200 000	500 000	29
1970	805 000	1 300 000	0
1971	290 000	1 300 000	0
1972	231 000	900 000	0
1973	170 000	-	0
1974	21 000	-	0
1975	425 000	-	0

[a] According to plan of operations (1968) for mass campaign.

Headquarters were established in Sana'a under the national programme director, Dr M.K. Al Aghbari, and in July a WHO epidemiologist arrived. Because of the paucity of health staff and facilities, the smallpox eradication programme was envisaged as one which would lay the foundation for other national communicable disease control activities.

A house-to-house vaccination campaign began in October 1969 and at first progressed reasonably well, with assessment showing more than 90% coverage. By the end of the year, 119 752 residents of Sana'a and 192 surrounding villages had been vaccinated, 25% of them for the first time; 80 000 people were vaccinated in other parts of the country. In 1969, 29 cases of smallpox were officially reported by the government to WHO, although at a WHO regional smallpox eradication seminar held in November of that year, the government submitted a report indicating that 47 smallpox cases had occurred. The WHO smallpox adviser in Yemen was asked to investigate and confirm these cases; he merely reported that he thought they were all cases of chickenpox. It was not long before the reliability of his observations was called into question when, in a quarterly report, he stated that, having examined the staff of the smallpox eradication programme, he had been able to ascertain that none were "carriers" of the disease. The quality of surveillance in Yemen did not improve materially thereafter.

In January 1970, when vaccination could be more readily performed than during the intolerably hot summer months, the vaccination campaign shifted to the coastal strip (Fig.

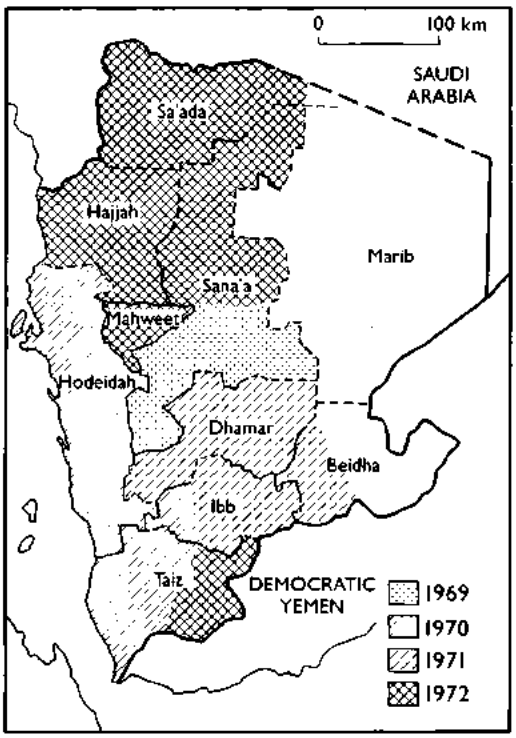

Fig. 21.2. Yemen: progress of the smallpox vaccination campaign, 1969–1972.

21.2). Three vaccination units, each equipped with a vehicle and consisting of a national supervisor and 8 vaccinators, proceeded systematically through the area performing house-to-house vaccination. Staff from the local health services, where such existed, worked with the teams in the expectation that they would continue maintenance vaccination after the teams had left. Each vaccinator averaged about 140 vaccinations a day. An assessment team checked vaccination takes and coverage 1 week later. By the end of the year, more than 800 000 people had been vaccinated.

Towards the end of 1970, the vaccination campaign began to deteriorate. Dr Al Aghbari was asked to assume direction of all preventive services for the Ministry of Health and was therefore obliged to spend less time in the field; project vehicles broke down more often and the field staff began to take increasingly frequent and extended holidays. The WHO adviser rarely left the capital city, and in March 1971 his assignment was terminated.

During the whole of 1971, only 290 000 persons were vaccinated; the level of coverage was unknown because assessment had ceased. The few reports of smallpox received were seldom investigated; the cases that were examined were diagnosed as chickenpox or dermatitis. The vaccination campaign was gradually extended to most other areas of the country and finally concluded in April 1973, although the inhabitants of most rural areas throughout the north and east remained unvaccinated. Only 231 000 persons were vaccinated in 1972, 45% of them for the first time. From the campaign's inception to its conclusion, the staff succeeded in vaccinating only about 2 million persons—less than half the estimated population. Of this number, nearly 300 000 were vaccinated by teams of the Swedish Save the Children Foundation, who were then providing health services in coastal areas of the country.

The government was dissatisfied with the programme and repeatedly requested the WHO Regional Office for the Eastern Mediterranean to assign another full-time WHO epidemiologist. This request was not met until April 1973, when the former WHO smallpox adviser in the Sudan, despite an unsatisfactory performance there, was transferred to Yemen. In addition to dealing with smallpox, he was made responsible for developing a preventive medicine section in the Ministry of Health and creating a health statistics unit.

About the time of his arrival, the systematic vaccination campaign was terminated and the teams were disbanded. Vaccination continued to be offered through existing health facilities. However, of the 170 000 recorded vaccinations in 1973, 60% were reported to have been given to adults who required international certificates of vaccination in order to leave the country.

None of the health units provided weekly or monthly reports of smallpox cases nor did they submit reports on other diseases. When suspected cases of smallpox were notified, national staff or the WHO epidemiologist investigated them and sent specimens to one of the WHO reference laboratories. In all, 26 specimens were submitted during the 7-year period 1971–1977. None contained poxvirus.

In 1975, a monthly communicable diseases reporting system was at last introduced and reports of smallpox and chickenpox were carried by hand to the capital. This was intended to facilitate investigation by the newly created Department of Preventive Health Services, consisting of a national medical officer, the WHO epidemiologist and

a clerk. Most of the reports received were from the 3 major towns. Five suspected cases of smallpox and 79 cases of chickenpox were reported in 1975 and 2 suspected cases of smallpox and 88 cases of chickenpox in 1976. None of them was confirmed to be a case of smallpox.

From 1970 to the end of 1977, neither WHO Headquarters staff nor the WHO regional smallpox adviser had devoted much attention or effort to the programme in Yemen. Smallpox eradication in other parts of the world commanded a higher priority. Because no confirmed cases of smallpox had been reported from Yemen since 1969 and none was being detected among the numerous pilgrims or Yemeni workers who travelled to Saudi Arabia and to other countries, WHO staff were cautiously hopeful that smallpox transmission had been interrupted.

By the autumn of 1977, when smallpox had been eliminated in Ethiopia (see below) and its interruption in Somalia was imminent, a more detailed appraisal of the situation in Yemen was considered to be essential. A WHO smallpox consultant who visited the country in September 1977 found large numbers of refugees from Ethiopia and some from Somalia living in villages along the coastal desert strip. Few had vaccination scars. An extensive vaccination campaign and search for cases were subsequently initiated in this area, but no cases were found.

In December 1977, another WHO consultant travelled through the highland areas, and, although he found no cases, he discovered that only people living in the larger towns and along the principal roads had been vaccinated during the campaign. Many of the more remote villages had not been visited by programme staff or vaccination teams for 6–8 years. If variola minor had been imported—from Ethiopia, for example—he believed that it might still be present, spreading slowly through sparsely settled areas, as had been the case in Ethiopia. Accordingly, it was deemed essential to conduct a thorough country-wide search for cases.

From June 1978 to the end of March 1979, a search programme under the direction of an experienced WHO epidemiologist, Mr Robert Steinglass, was conducted by Yemeni staff assisted by personnel of the Swedish Save the Children Foundation and Peace Corps volunteers from the USA, who were engaged in other health programmes in Yemen at that time. Three surveillance teams, each consisting of a team leader, 1 or 2 surveillance workers, a driver and locally hired temporary staff searched 146 of 162 districts and 920 villages and towns with a population of more than 500 persons. In all, 116 184 persons were examined in villages and towns whose total number of inhabitants amounted to 897 488—i.e., 13% of Yemen's resident population. Four hundred and eighty reports of illness with rash and fever were investigated; 43 specimens were submitted for laboratory examination, but none showed evidence of smallpox.

Vaccinial immunity was low, as had been expected. Only 23% of children under 4 years of age and only 63% of the population as a whole had vaccination scars (Table 21.3).

Of 2514 persons with the facial pockmarks of smallpox none was younger than 11 years of age and none had experienced smallpox

Table 21.3. Yemen: results of vaccination scar survey, by governorate and by age, 1978–1979

Governorate	Age-group (years)							
	0–4		5–9		⩾10		Total	
	Number examined	% with scar	Number examined	% with scar	Number examined	% with scar	Number examined	% with scar
Sana'a	2 849	33	14 219	73	13 837	84	30 905	70
Hodeidah	2 619	42	7 378	77	9 996	84	19 993	77
Taiz	3 371	30	10 419	68	6 591	71	20 381	56
Ibb	3 694	27	7 039	72	4 498	73	15 231	66
Dhamar	2 099	20	3 241	61	3 011	76	8 351	63
Hajjah	1 964	9	4 617	59	4 719	77	11 300	59
Sa'ada	698	12	1 320	59	1 347	82	3 365	64
Mahweec	1 079	8	2 001	57	1 741	79	4 821	60
Beidha	392	19	672	53	568	73	1 632	54
Marib[a]	1	–	95	38	109	64	205	50
Total	18 766	23	51 001	66	46 417	73	116 184	63

[a] The Governorate of Marib (population 40 896) was not accessible to government staff and thus area-wide search was not possible.

after 1969. Persons with facial pockmarks were found in 95% of the 146 districts and in 72% of the villages. More than 60% had contracted the disease during the 1957–1963 epidemic.

It had been feared that smallpox eradication in Yemen would present a formidable problem; ironically, the last known cases had occurred just before the mass vaccination campaign began in October 1969. Natural immunity conferred by the extensive epidemic of variola major in 1957–1963, coupled with the practice of variolation, apparently served to reduce the number of susceptible subjects to a sufficiently low proportion of the population that transmission ceased. It is possible that undetected importations, notably from Ethiopia, Yemen's nearest endemic neighbour, may have occurred, but if so they terminated spontaneously. Whatever its problems, the programme served eventually to foster an infectious disease reporting system and provided an impetus to a broader immunization programme, which commenced in 1977.

DEMOCRATIC YEMEN

Democratic Yemen occupies a vast barren area in the south-western part of the Arabian Peninsula, but as was revealed in its first census in 1973, 55% of the country's population of 1.6 million lived in 12% of the land area in and around Aden, the capital. In 1967, Democratic Yemen was considered to be free of smallpox, the last endemic case having occurred in 1960. However, it was thought to be at high risk of importations. Ships carrying Mecca pilgrims from Asia and Africa regularly called at Aden; and travellers as well as refugees, especially from areas of Ethiopia with endemic smallpox, were numbered in the tens of thousands. Accordingly, a WHO-supported programme was planned for Democratic Yemen.

Until it achieved independence in 1967, the area constituting Democratic Yemen consisted of the British crown colony of Aden and a large number of loosely federated independent sultanates and sheikdoms, known as the Protectorate of South Arabia. Over past decades, occasional small outbreaks of smallpox, usually attributed to cases imported by pilgrims, had been reported from Aden. The last officially notified outbreaks occurred between 1957 and 1961, during which 341 cases with 105 deaths were recorded, primarily in the western part of the country. The outbreaks were said to have resulted from a series of different importations from India, Pakistan and Yemen. They were controlled by mass vaccination. Twenty-four cases of variola minor, which were not officially reported to WHO but were nevertheless recorded in a government document, occurred in 1965 in the eastern part of the country. As in other countries, there were undoubtedly other unreported cases, but in this very sparsely settled area it was difficult for smallpox transmission to be sustained; any importations that may have occurred ceased spontaneously.

Vaccination with liquid vaccine had been fairly extensively practised in the British crown colony of Aden for many decades. In the less populated areas to the east, protection against severe smallpox was more frequently achieved by variolation. The outbreaks of 1957–1961 had occasioned an extensive vaccination campaign in Aden, some 338 000 vaccinations having been recorded between 1957 and 1959. In 1960, freeze-dried vaccine was first made available by UNICEF for a vaccination campaign, but until 1970, it was uncommon for more than 50 000–75 000 persons to be vaccinated each year.

In September 1969, WHO agreed to support an eradication programme, basically a village-by-village campaign to administer smallpox vaccine to all persons and BCG vaccine to those under 15 years of age. WHO supplemented the salary of the national programme director, paid the national staff a per diem, provided vehicles, vaccine and other supplies and equipment, and made funds available for petrol and vehicle repairs. WHO eventually provided about US$206 000 and more than 1.8 million doses of vaccine in support of the programme (Table 21.4).

The national staff comprised 48 persons, including 32 vaccinators who worked in 4 operational groups, each with 4 vaccination teams consisting of 2 men. The vaccination campaign proceeded on a house-to-house basis and was regularly assessed by a special team. Because of security problems, operations were initially restricted to 3 of the country's 6 governorates that were located in the immediate vicinity of Aden. In September 1971, one of the programme vehicles, carrying 10 vaccinators and the driver, was destroyed by a land-mine, which killed 4 of the vaccinators and injured the others. Under-

Table 21.4. Democratic Yemen: WHO support provided to the smallpox eradication programme, 1967–1979

Year	Personnel, supplies and equipment (US$)	Doses of vaccine (thousands)
1967	–	–
1968	–	150
1969	22 941	35
1970	17 801	–
1971	22 297	350
1972	1 100	–
1973	26 174	220
1974	17 000	602
1975	17 000	–
1976	17 000	300
1977	15 005	–
1978	49 584	96
1979	328	62
Total	206 230	1 815

standably, the staff feared to venture too far from the capital. Not until 1973 did civil disorder subside sufficiently to permit the extension of vaccination activities into all governorates.

As is shown in Table 21.5, the number of vaccinations performed annually from 1970 onwards ranged between 169 364 (1971) and 302 296 (1973). Productivity was not high, each vaccinator averaging about 50 smallpox vaccinations and 10–20 BCG vaccinations a day. This was partly attributable to the difficulty of travelling through the generally rugged mountainous country, with few roads. Assessment figures indicated that the coverage achieved was consistently about 90%, but it took 7 years for a total of 1.5 million vaccinations to be performed, a number approximately equivalent to the population. During this time, some 514 000 BCG vaccinations were also administered.

Despite the strategic location of Democratic Yemen and the apparent risk of importations, no cases were confirmed after 1967. A single case in Aden was reported to WHO in 1968 but the report was later retracted in the belief that the illness had been chickenpox. The absence of known importations can be explained in part by diminished maritime traffic associated with the closure of the Suez Canal from 1967 to 1975 and in part by restrictions on travel imposed by the government after independence in November 1967. Conceivably, outbreaks may have been overlooked since neither a surveillance nor a morbidity reporting system was ever developed. However, extensive surveys conducted during the country's programme in 1978 to certify the absence of smallpox failed to detect any person who had been infected with the disease since 1966. These surveys also showed that, in the different governorates, between 76% and 90% of the population had vaccination scars—a high level of vaccinial immunity.

Table 21.5. Democratic Yemen: number of vaccinations performed and number of reported cases of smallpox, 1967–1975

Year	Number of vaccinations	Number of reported cases
1967	10 830	0
1968	46 720	0
1969	26 233[a]	0
1970	302 202	0
1971	169 364	0
1972	245 628	0
1973	302 296	0
1974	181 277	0
1975	242 881	0

[a] Six months only.

Contrary to expectations when the programme began, Democratic Yemen did not experience problems with smallpox; in retrospect, a special vaccination programme may have been unnecessary. However, the combined smallpox and BCG vaccination campaign did provide a basis for the establishment of a national immunization programme.

ETHIOPIA

Ethiopia was 6 times larger in area (1.2 million square kilometres), with a population (25.5 million in 1970) more than 5 times greater than that of Yemen, but the problems of geography and population dispersion were similar. Most of Ethiopia's population was widely distributed in small groups of huts scattered across the central highlands (Fig. 21.3) at 1500–3000 metres above sea level. Rugged mountains and deep ravines made travel extremely difficult throughout this area, and impossible during the rainy season, from June to September. At the periphery of the country were lowland areas in the west and south-west, with a fertile and more populated savanna grassland. Nomads roamed the vast Danakil and Ogaden deserts to the east, moving freely across the unmarked borders with Somalia and the French Territory of the Afars and the Issas (later Djibouti). Less than 10 000 kilometres of all-weather roads connected the few scattered cities and towns. Health facilities and trained health

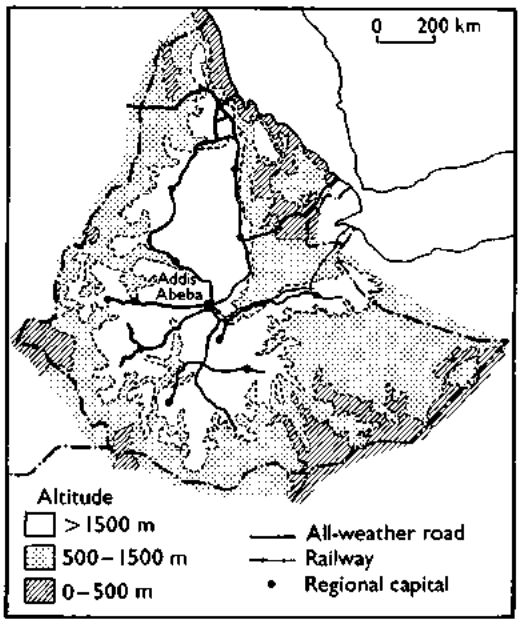

Fig. 21.3. Ethiopia: topography and road system.

staff were few; vaccination was all but unknown to most of the population, but variolation was widespread. Several hundred cases of smallpox were reported each year, but in 1967 it was surmised that thousands of cases must be occurring.

Throughout the world, experience had shown that smallpox transmission was not readily sustained in sparsely settled areas. Elimination of smallpox from urban centres and the accessible, more populated rural areas usually resulted in the disease dying out spontaneously in the more remote parts of a country. In Ethiopia, this did not happen. Here, among a dispersed, thinly settled population, the global eradication of smallpox came nearest to being thwarted, as an unparalleled array of problems and catastrophes continually hampered the programme. Nearly 6 years elapsed after the campaign had begun before the last outbreak was finally discovered and contained, in August 1976.

A detailed account of the programme is presented in the book *Smallpox Eradication in Ethiopia* by Tekeste et al. (1984), from which most of the data in this chapter are drawn.

Background

Ethiopia, in 1967, was one of the world's least developed countries, and until 1974 it was a monarchy with numerous feudal landlords. The infrastructure of services for health, education, transport and communications was rudimentary except in the northern province of Eritrea, in which a number of roads and health centres had been built during the Italian and British administrations.

Administratively, the country was divided into 14 provinces (which, after the 1974 revolution, became 15 regions), each with a governor, who was usually a member of the royal family. Each province was subdivided into *awrajas* (102 in the country as a whole) and these, in turn, into *woredas* (539 all told), each with its appointed governor or administrator. At the local level, the feudal, often absentee, landlord was the acknowledged headman, but he was frequently indifferent and sometimes hostile to higher government authority. To obtain assistance with the programme at each administrative level a special letter requesting cooperation had to be prepared by a superior and taken by messenger to the official concerned.

No census had ever been taken but it was thought that no more than 2 million of the estimated 25.5 million population lived in about 200 towns and villages of 500 or more persons. In the rural areas of the plateau, the houses were widely scattered. There, the smallest traditional unit, sometimes referred to as a village, was the *mender*, consisting of up to 100 houses occupied by one or more related families. Fifty or more *menders* comprised a *deber*, which included the membership of a single church. After the 1974 revolution and nationalization of the land, workers' cooperatives, called "farmers' associations" or "urban dwellers' associations", were created and village areas were defined. The villages, however, were unlike those in most other countries in that they usually extended over large areas, the distance between houses often ranging from a few hundred to a thousand metres. In the extensive eastern and southern scrub desert areas, which comprised half the country, nomadic groups with ethnic ties to the neighbouring French Territory of the Afars and the Issas and Somalia wandered freely, not infrequently crossing open borders between the countries. In the south-west were tribal groups whose way of life was little more advanced than that of a Stone Age culture.

Roads of any type were few; more than 85% of the population lived further than 30 kilometres away from the nearest all-weather road (Ayalew, 1982). Travel from place to

place during the dry season was largely on horse- or muleback or by foot. When torrential rains occurred in the highlands, between June and September, large areas became completely inaccessible. Communications were poor: an unreliable, frequently unusable, telephone service linked the capitals of provinces, and the postal service was deficient.

Language presented a further problem. The people of Ethiopia consisted of 10 major ethnic groups speaking 70 languages and dialects. Frequently, programme staff had to communicate successively through two or three different interpreters to question villagers about the existence of smallpox and to explain the unfamiliar practice of vaccination. Some people were reasonably receptive, but refusal and sometimes active resistance were encountered among many who lived in the highland areas in the north and central parts of the country. Not surprisingly, smallpox proved to be particularly tenacious in those areas.

Health personnel and facilities in 1967 were concentrated in Addis Abeba, the capital, and in Eritrea. The largest proportion of the government's health budget was allocated to curative services, to which not more than 5% of the population had access. Government records for 1967 show a census of 84 hospitals and 64 health centres and a total of 362 physicians and 2800 other health staff. For 40% of the population, a journey of 3 days or more, and for another 30%, a journey of 1–2 days, was required to reach the nearest health unit. Personnel engaged in the administratively separate malaria eradication programme were far more numerous than the national health services staff. In all, 8000 malaria eradication staff were distributed over about one-third of the country. They were concerned only with malaria and were supported under a bilateral assistance programme.

Protection against smallpox was often provided through variolation. This was usually performed by the head of a household among family members after cases began to occur in the vicinity. The Afghan type of professional variolator, who travelled widely and preserved scabs and pustular material over long periods of time, was uncommon. Data on the number of smallpox vaccinations performed annually before 1971 are not available but estimates indicate the total to be less than 500 000. Most of them were performed in hospitals and clinics; a few were given by an "Anti-epidemic Service", a small mobile unit which vaccinated people in and around Addis Abeba when outbreaks were reported. The vaccine, which had been produced at a government laboratory in Addis Abeba since 1953, was of the thermolabile liquid variety. In the mid-1960s, however, the preparation of a freeze-dried vaccine began, but this could not be tested for potency owing to a lack of fertile eggs. When it was eventually examined by a WHO reference laboratory, it was found to be unsatisfactory. In 1970, freeze-dried vaccine was provided by WHO and vaccine production in Addis Abeba ceased.

Little is known about the prevalence, extent and severity of smallpox before 1971. Epidemics with high mortality were said to have occurred every 10–30 years during the 19th century. Annual statistical compilations that date from 1931 show as many as 2832 cases in 1956 but comparatively few in most years. The cases that were reported were among hospitalized patients in the few urban

WHO / T. FARKAS

Plate 21.1. A variolator in Ethiopia obtaining pustular material from a patient (*lying*) and inoculating it into the arm of a healthy recipient (*standing*). Variolation was usually performed by one of the elders in a family and was widely practised throughout Ethiopia. The last known patient in Ethiopia (August 1976) developed illness following variolation. (Detail from a painting by Zerihun Yetmgeta presented to WHO by the Government of Ethiopia.)

Variolation and Receptivity to Vaccination

Smallpox was widely recognized and feared by the different ethnic groups throughout Ethiopia, each of which, in the absence of vaccination, dealt with it in a different manner. Among the Amharas, who largely populated the central zone provinces and Shewa, and among the nomads of the eastern desert areas, protection was obtained through variolation, which was practised widely when outbreaks occurred. Many Amharas resisted vaccination in favour of variolation and religious ceremonies that consisted in decorating the dwelling of a patient with fresh green leaves, grasses and flowers and in burning incense. Sheep, goats and hens of different colours were sacrificed and ritual play-acting and singing were performed to induce the disease to take a mild form. Other groups had other practices and rites. When smallpox occurred, the Nuers, a Nilotic tribe living near the Sudanese border, performed a ceremony in which a prophet would lead the people to a river where goats were sacrificed to the "mother of gods", who was thought to live in the river; in a ceremony of joy, the assembled crowd would then bathe in the river.

For reasons which are unclear, most ethnic groups in the south and east of the country readily accepted, indeed actively sought, vaccination whether or not they performed variolation. Among Galla groups, who inhabited large areas of provinces in the south-west and south-east, people returned many times for vaccination, and many villages reported falsely that outbreaks were occurring in order to induce the teams to visit. In this area, it was not uncommon for teams to discover crudely scribbled notes left along trails requesting visits to villages as distant as 40–50 kilometres.

centres. There is no information on the number of deaths. After 1971, when the eradication programme began and more complete data became available, only the mild variola minor form of smallpox was found. Variola major had disappeared, but it is not known when this occurred. Variola minor was documented as early as 1958, but as recently as 1964 a smallpox outbreak with a high case-fatality rate typical of variola major was reported by a health officer in the central highlands.

Delays in Launching an Eradication Programme

At the inception of the Intensified Smallpox Eradication Programme in 1967, Ethiopia was considered to be strategically important as an endemic country. The neighbouring areas of the French Territory of the Afars and the Issas, Somalia and the Sudan were thought to be free of smallpox. Kenya, with an extensive network of health services and a more complete notification system, was reporting fewer than 200 cases a year. If reinfection of adjacent countries was to be averted, a programme would have to be started in Ethiopia as soon as possible.

Government officials stated, however, that they were not interested in undertaking a smallpox eradication programme and could not do so because so many resources were already committed to malaria eradication. They reasoned that one eradication programme must be as expensive as another, a belief encouraged by expatriate malaria advisers. Given that the Ethiopia malaria eradication programme was then disbursing more than US$8 million a year, primarily from bilateral contributions, and that it employed 8000 workers, their apprehension was understandable. The government authorities did not appreciate that a smallpox eradication programme was far simpler, cost much less and required far fewer personnel than a malaria eradication programme. Moreover, WHO staff believed that smallpox eradication in Ethiopia might be combined successfully with other health activities then being considered, including a BCG vaccination programme in urban areas and a proposed yellow fever vaccination campaign which the Federal Republic of Germany was expected to support. The most extensive resources available were those of the malaria eradication programme itself. It was felt that much could be accomplished if its directors would permit the thousands of malaria workers to serve as smallpox surveillance agents and to vaccinate those encountered during their regular house-to-house visits. In addition, several

projects staffed by United States Peace Corps volunteers were then in operation in Ethiopia and it was understood from United States government officials that they would be receptive to a request to provide manpower to health-related projects.

WHO smallpox eradication staff believed that a suitable, economically feasible and acceptable plan for at least a control programme, if not for eradication, could be developed. To do so would require appraisal and discussion in Addis Abeba of potentially available resources and of the cost and options for the conduct of such a programme. Repeated proposals were made to the government that WHO regional and Headquarters staff should make an exploratory visit, but for nearly 3 years these proposals were firmly declined. Initially, this reaction was difficult to understand because most governments were more than willing to discuss possible options, whether or not they were inclined to undertake a programme. Gradually, however, it became known that the United States malaria eradication programme adviser and his Ethiopian counterpart had persuaded the Minister of Health that a smallpox eradication programme would fatally compromise the malaria eradication campaign, which was then making little progress. They advised that, under the circumstances, his best approach would be to refuse to receive WHO smallpox eradication staff, even for exploratory discussions.

The impasse was not readily resolved. The strategy and the projected order of magnitude of needs for smallpox eradication were discussed in Geneva at the World Health Assembly with Ethiopian government officials and malaria advisers from the USA, with bilateral assistance staff in Washington and with malaria staff at the United States Center for Disease Control—all to no avail. An indirect approach to the government was planned when Dr George Lythcott, senior adviser to the United States-aided western and central African smallpox eradication programme, was invited to speak about that programme at a meeting of the Organization of African States in Addis Abeba. Having been briefed by WHO staff and being prepared to hold informal meetings with Ethiopian government officials, he was about to leave for Addis Abeba when United States officials abruptly and without explanation cancelled his trip.

Nearly 3 years had elapsed when, inexplicably, in October 1969, the government responded favourably to yet another proposal for an exploratory visit. Dr Ehsan Shafa, then Regional Adviser on Smallpox Eradication at the WHO Regional Office for the Eastern Mediterranean, and Henderson flew immediately to Addis Abeba. The response to the proposed visit had been sent by a subordinate when the Minister and Secretary of Health were absent on a trip abroad. They were not pleased, on their return, to find the WHO team awaiting them; they made it clear that Ethiopia's attitude had not changed. They did agree, however, that Henderson and Dr Shafa could devote 2 weeks to the preparation of a plan which the government would consider. In view of WHO's budgetary limitations and the obvious antipathy of the government, it was apparent that whatever programme might be devised would have to be a modest one. The malaria eradication programme's considerable resources in manpower and transport offered a potential building block, but its director declined to cooperate in any way. There were no other immunization programmes and little assistance could be expected from the few existing health units. However, tentative offers to provide volunteers were made by the USA and Japan. Among the many officials to whom Henderson and Dr Shafa spoke was Dr Kurt Weithaler, then serving as director of

BY COURTESY OF D. A. HENDERSON, 1971

Plate 21.2. Kurt L. Weithaler (b. 1919), an experienced health administrator, served as the senior WHO adviser to the Ethiopian smallpox eradication programme from 1970 to 1976.

the hospital for the Emperor's Imperial Guard. Dr Weithaler, an Austrian, had been employed by the government for more than a decade, was widely known in government and medical circles, served as a member of the Health Minister's advisory panel the General Medical Board—and was a friend of the Emperor. He expressed considerable enthusiasm for the programme and intimated that he might be persuaded to serve as WHO's senior adviser. The draft plan of operations was presented to the Minister on a Saturday for consideration that weekend and a decision on Monday. He expressed little interest. Meanwhile, unbeknownst to the WHO team, Dr Weithaler showed the plan to the Emperor, who agreed that it should be initiated and ordered the Minister of Health to support it.

The Programme Begins, 1971

The draft plan of operations envisaged: (1) a search for outbreaks and their containment to the extent possible with the available manpower; (2) the development of a simple surveillance programme for the reporting of cases and vaccination by the staff of existing health facilities; and (3) mass vaccination in Ethiopia's few centres of population. It was hoped that, with the limited personnel and equipment that could be provided, smallpox transmission might be successfully interrupted in the accessible areas. It was to be hoped that the disease would then die out spontaneously in at least some of the rural areas. However, since a relatively small proportion of the population lived in accessible areas and since vaccinial immunity was undoubtedly as low as anywhere in the world, the proposition was uncertain. All the same, a less than fully effective control programme was better than no programme at all.

A staff of about 70 was envisaged. The government requested that a senior WHO medical officer should be appointed as "the responsible executive authority", and the energetic Dr Weithaler was recruited to fill the post. It was exceptional in most countries for a person assigned by WHO to serve in this capacity but, in Ethiopia, in which trained personnel were in short supply, such an appointment was considered essential. A WHO epidemiologist was to be appointed for surveillance, and Dr Ciro de Quadros, who had served previously on the national staff of the Brazilian smallpox eradication programme (see Chapter 12), was selected for this post. The government assigned as the senior national professional Ato Tamiru Debeya, a respected and able person who retained this responsibility through 1975. His title was that of sanitarian but, in Ethiopia at that time, such persons had a broad public health training and served as administrators for many public health programmes. Twelve other workers were to be assigned to the headquarters office—3 drivers, 8 office staff and a most competent locally recruited WHO administrative officer, Ato Tefari Seyoum. For assignment to the field, the government agreed to provide 21 staff, health officers or sanitarians, who would work with volunteers from the USA. The health officers played an exceptionally important role; they were graduates of a recently established 4-year course of study in the health sciences which was designed for students who had completed secondary school.

Ethiopia's financial commitments consisted only in paying salaries of its health officers and sanitarians, all of whom were transferred from other programmes, and meeting the cost of office accommodation. WHO provided all supplies and equipment and covered the cost of transport, as well as

E SHAFA, c. 1973

Plate 21.3. Ciro C. A. de Quadros (b. 1940) worked in the smallpox eradication programme in Brazil before joining WHO and the programme in Ethiopia, 1970–1976. In 1977, he became regional adviser for the Expanded Programme on Immunization in the Americas.

the per diem allowances of Ethiopian staff and the salaries of the central office staff. The salaries and expenses of the volunteers were borne by their respective governments. WHO provided, in all, US$175 562 in 1969–1970, in addition to supplies of vaccine (Table 21.6). Eventually, the Organization was to spend nearly US$13 500 000 from its regular budget and from contributions made by numerous governments to the WHO Voluntary Fund for Health Promotion and to contribute more than 23 million doses of vaccine. The Ethiopian government spent US$1 360 546. Additional support, amounting to about US$1 390 000 was provided, in cash and in kind, through bilateral contributions from Austria, the Federal Republic of Germany, Japan and the USA. The total support to the programme amounted to about US$0.57 per head of population.

During the autumn of 1970, personnel were recruited, the volunteers from the USA arrived, equipment was delivered, a central office was established, training programmes were conducted, and by mid-January 1971, field operations began. At that time, there were only 3 other countries in Africa in which smallpox remained endemic—the Sudan, Zaire and South Africa. The latter 2 succeeded in interrupting transmission in 1971 (see Chapters 18 and 20).

For a programme in one of Africa's last endemic countries—one of its largest and least developed—the available resources were few indeed. Over the first 6 months, the entire field staff consisted of only 39 persons—the 2 WHO advisers, 2 health officers, 19 sanitarians and 16 United States volunteers. They had only 6 Land Rovers between them, although 11 more were scheduled for delivery that summer. In the interim, it was hoped that vehicles might be borrowed from the malaria eradication programme's large reserve pool of vehicles, which were parked at a training centre south of Addis Abeba. A request was made, but the vehicles mysteriously vanished. The request was denied on the grounds that all vehicles were in use. (It was later learned that they had been transferred to a motor pool in a remote desert area.)

It was decided to concentrate personnel and vehicles in the 4 provinces of the south-western zone: Gamo Gofa, Kefa, Ilubabor and Welega (Fig. 21.4; Table 21.7). Besides being epidemiologically important because they bordered on the Sudan, these provinces had a better health service structure than most, and the people's acceptance of vaccination was generally good. Two additional vehicles and teams were assigned for work in Addis Abeba and the surrounding Shewa Province. One sanitarian was assigned to each of the other provinces to establish a smallpox eradication programme office in or near the office of the provincial medical officer. His duties were to report weekly any cases of smallpox that were discovered, to compile a list of health facilities, and to visit them, by bus or mule, in order to provide vaccine and to encourage them to report cases and to vaccinate. In the 4 priority provinces, these functions were to be undertaken by the teams,

Table 21.6 Ethiopia: WHO and government support to the smallpox eradication programme, 1969–1979 (US$)[a]

Year	Expenditure by WHO			Expenditure by government	Vaccine (thousands of doses)
	Personnel, supplies and equipment	Local costs	Total		
1969	43 236	-	43 236	-	-
1970	121 233	11 093	132 326	-	315
1971	141 125	120 000	261 125	73 150	4 323
1972	329 506	130 150	459 656	79 511	2 432
1973	316 197	220 000	536 197	90 679	1 998
1974	318 493	403 250	721 743	107 033	2 468
1975	1 184 840	561 400	1 746 240	118 715	2 384
1976	2 663 490	1 399 218	4 062 708	200 779	5 720
1977	1 556 977	1 274 309	2 831 286	221 660	3 048
1978	455 999	697 384	1 153 383	228 699	560
1979	224 549	1 308 576	1 533 125	240 350	25
Total	7 355 645	6 125 380	13 481 025	1 360 546	23 273

[a] An additional US$1 390 213 were provided through bilateral assistance.

which were also expected to carry out an active search for cases and to contain by vaccination any outbreaks that were found.

To provide encouragement and guidance to the smallpox eradication staff and other health personnel throughout the country, Dr de Quadros, in January 1971, inaugurated the publication of a surveillance report which documented smallpox incidence and conveyed important information and instructions. The report was at first distributed monthly to health personnel and relevant government officials throughout the country; late in 1974, weekly publication began. The report proved of inestimable value in securing cooperation and support and also served to sustain morale among the widely distributed smallpox eradication staff, who could contact each other only infrequently.

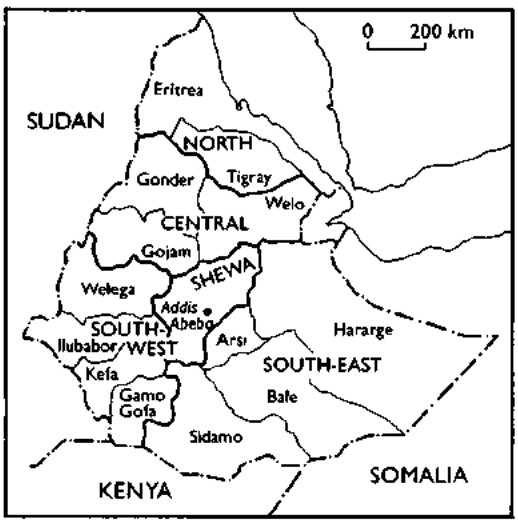

Fig. 21.4. Ethiopia: zones and provinces, 1970.

The number of cases that might be discovered when the teams reached the field was a subject of intense speculation. Ethiopia had reported only 197 cases in 1969 and 722 cases in 1970. It was recognized that smallpox was greatly underreported, but the extent of the underreporting was unknown. Although few vaccinations were being performed, variolation had been extensively practised throughout the country and had undoubtedly rendered many persons immune. To obtain some idea of the possible extent of smallpox, Henderson and Dr Shafa, during their visit in 1969, had questioned many health officers, mission health personnel and others, both in Addis Abeba and on a field visit to Welega Province. Surprisingly, few persons reported having seen many cases of smallpox recently and some reported having seen no cases whatsoever for many years. Although the survey was brief and incomplete, it fostered the hope that smallpox might be uncommon in the sparsely settled rural areas and that continuing endemic transmission might be confined primarily to the comparatively few populous areas.

Whatever the smallpox situation may have been in 1969, it differed greatly in 1971 from

Table 21.7. Ethiopia: demographic data, by zone and province and number of health facilities, 1971

Zone/province	Estimated population[a] (thousands)	Persons per km²	Towns with 2000 or more inhabitants	Number of hospitals, health centres and clinics
NORTH				
Eritrea	2 125	18	20	141
Tigray	1 892	29	18	77
CENTRAL				
Gojam	1 784	29	11	57
Gonder	1 797	24	11	73
Welo	2 286	29	11	86
SOUTH-WEST				
Gamo Gofa	876	22	7	56
Ilubabor	681	14	6	58
Kefa	1 414	26	6	70
Welega	1 768	25	9	89
SHEWA	5 565	65	36	177
SOUTH-EAST				
Arsi	954	41	10	51
Bale	768	6	5	39
Hararge	2 736	10	15	123
Sidamo	2 457	21	18	102

[a] Ethiopian government estimate for 1971. United Nations (1985) data show a total population of 26 133 000 for Ethiopia in 1971.

Smallpox Surveillance and Containment in the South-west Zone in 1971

One volunteer, Mr Vincent Radke, has described his own initial surprise at the magnitude of the smallpox problem and the necessary adaptations in procedures which field staff had to make. During the training programme, the surveillance teams had been instructed to undertake a planned series of trips through the province for which they were responsible. They were to visit health centres and schools, where these existed, as well as village leaders and, in showing the WHO smallpox recognition card, were to inquire about possible smallpox cases. Any reports were then to be investigated. In the first classroom Mr Radke visited in Kefa Province, he obtained so many reports of cases in so many different villages that he did not bother to visit the other classrooms but went immediately to investigate. Village after village throughout many parts of this and other south-western provinces were found to be so heavily infected with smallpox that he and his fellow-workers decided that for some areas, even village-by-village containment vaccination was futile. Instead, they began to try to define the outer limits of the spreading epidemic and to concentrate on vaccination in populations at the circumference of the outbreak area, much as one would fight a forest fire.

what had been expected. The teams began work in mid-January and discovered 278 cases in only 2 weeks; 1493 cases were found in February and 3434 cases in March. This amounted to half the cases being reported throughout the world at that time. Henderson was sceptical that so few field staff could discover and investigate so many cases; he therefore cabled Dr Weithaler and Dr de Quadros, cautioning against recording rumoured outbreaks without due investigation. They were justifiably indignant and replied by cable and letter that the only cases reported were those individually confirmed by the smallpox eradication staff. Dr de Quadros had established a reporting system which was similar to that used in Brazil. A form was completed for each household in which a case was discovered. The form included the name, age, sex and past history of smallpox and vaccination of each household member. Only the cases seen by the surveillance teams and recorded on the forms were reported. The Ethiopian programme, in fact, had the most comprehensive data collection system of any national eradication programme and was the only one in which data were collected from the outset.

Since vehicles were available only to the teams in the south-western zone and Shewa during the first 6 months, it was not expected that the health officers and sanitarians assigned to other provinces would undertake much field work. However, most of them exhibited extraordinary ingenuity in getting from place to place by bus and borrowed vehicles, by foot and by mule. They, too, discovered and investigated numerous cases of smallpox.

Up to the end of June 1971, the field staff of only 39 persons documented 13 447 cases, more than had been recorded in the whole of India during the preceding year. Meanwhile, the threat that Ethiopia represented to its smallpox-free neighbours became manifest in March, when an outbreak of 46 cases of smallpox, introduced by an Ethiopian cattle herder, was discovered in Kenya. The now evident epidemic smallpox and the concern shown by neighbouring countries served to alarm the government, and from then on the programme began to receive somewhat greater support.

Seasonal torrential rains began throughout the highlands in June and, until September, forced the surveillance teams to restrict activities to populations living along the few all-weather roads. There, in addition to a search for cases, extensive systematic vaccination campaigns were conducted in the towns and cities. In Addis Abeba itself, smallpox eradication staff, with help from the Anti-epidemic Service and 12 secondary-school students, vaccinated 154 000 people over a 2-month period.

It was apparent that the problem in Ethiopia was a major one, requiring far greater resources than were available. Efforts were intensified to find such support. The government agreed to provide some additional staff but, in fact, had few available who could be mobilized except for personnel

WHO/P. ALMASY

D. PIBURN

Plate 21.4. Ethiopia. **A:** The rugged terrain required extensive travel on foot and muleback and eventually necessitated the use of helicopters. **B:** Roads were few and sometimes impassable, but the bridge shown here was crossed 4 times in 1974.

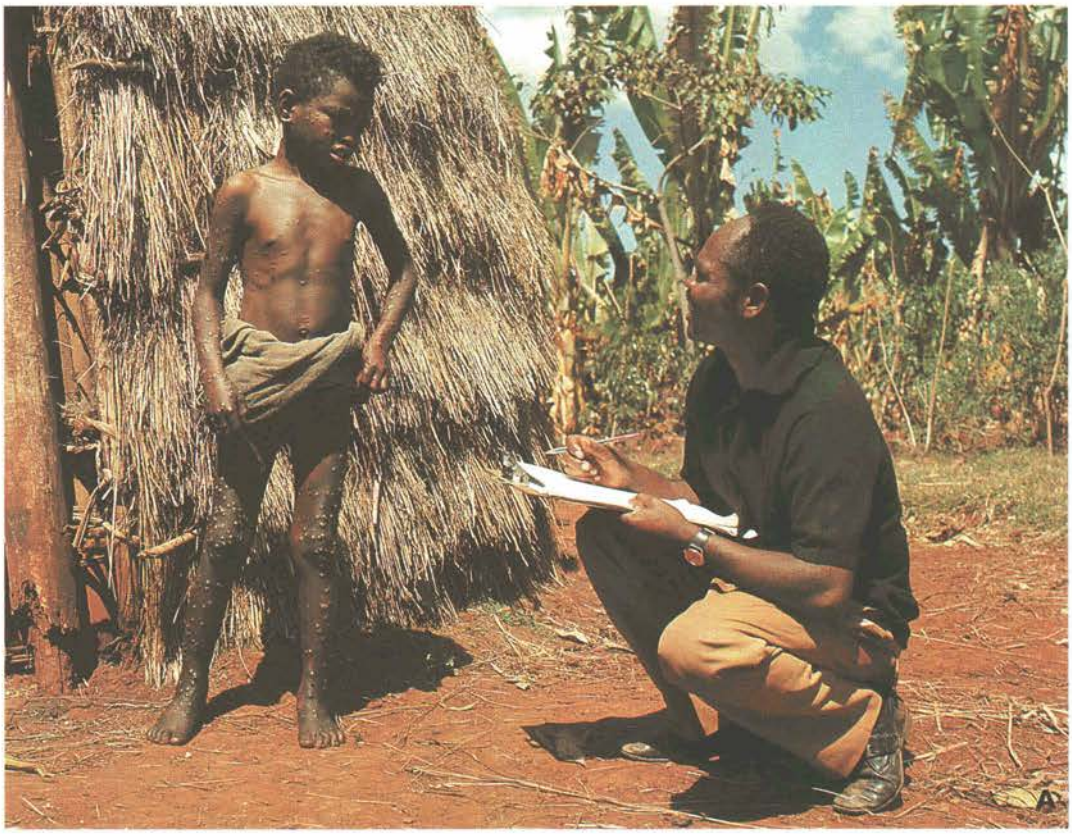

Plate 21.5. **A:** An Ethiopian sanitarian, Assefa Gobeze, records information about a typical case of smallpox. **B:** Dimo village, Bale Region, was the site of the last outbreak of smallpox in Ethiopia in August 1976.

J. J. A. NIEMEIJER, KEFA REGION, 1972

Plate 21.6. Vincent J. Radke (b. 1948) was one of 16 United States Peace Corps volunteers recruited in 1970. He worked for the eradication programme in Ethiopia for 4 years.

of the malaria eradication programme, but a request for the transfer of some of these staff was refused. Programme funds previously destined for countries in the WHO African Region were transferred to Ethiopia, as well as what little remained for smallpox eradication in the WHO Voluntary Fund for Health Promotion. Other Headquarters funds for 1972 were earmarked for the recruitment of another WHO epidemiologist, Dr P. A. Koswara, formerly the director of Indonesia's successful programme. Continuing discussions with the government of Japan led to its commitment to provide 30 transceivers as well as 5 vehicles and 12 volunteers to serve as radio and automobile mechanics. The Austrian government agreed to provide 4 volunteers, and the USA to increase the number of its volunteers.

The end of the seasonal rains and the return of the teams to the field were eagerly awaited. During the rainy season in other parts of the world, smallpox was transmitted much less easily, and with travel restricted, the disease often died out in large areas. Moreover, the number of susceptible individuals was clearly lower than in the previous year because of the extent of the epidemics and the large-scale vaccination–containment activities that had been conducted in urban areas during the rainy season and in rural areas earlier in the year. Any hope that the smallpox problem might soon become more manageable vanished, however. The number of cases discovered totalled 2113 in September and rose each month, reaching 3322 in December.

In 1971, 26 329 cases were recorded, more than half in Shewa and the 4 provinces of the south-west zone, in which reporting was the best (Table 21.8). Cases were detected in 146 of the country's 539 *woredas* in the first half of the year, and in 160 *woredas* in the latter half (Fig. 21.5). In all, 3.1 million vaccinations

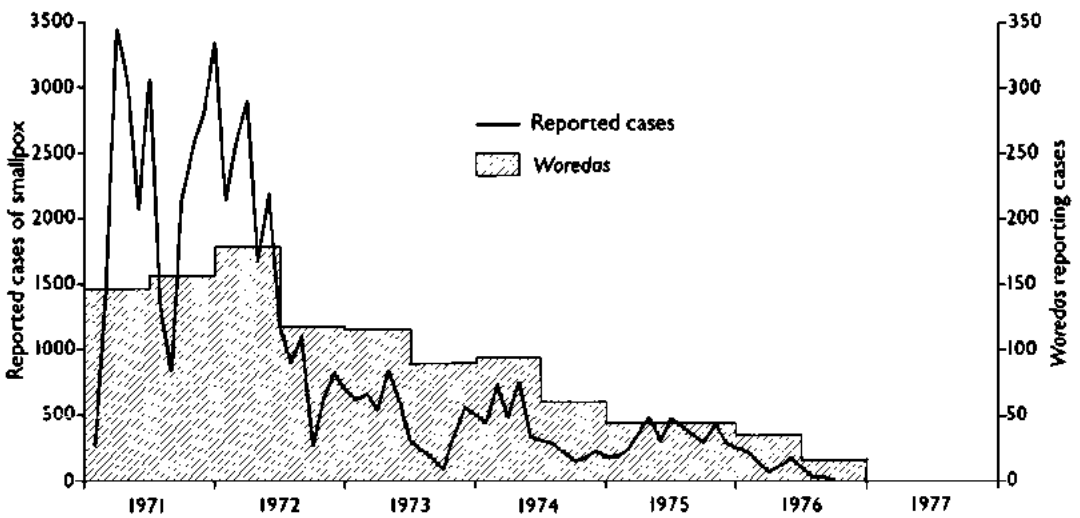

Fig. 21.5. Ethiopia: number of reported cases of smallpox, by month, and number of woredas reporting cases, by 6-month period, 1971–1977.

Table 21.8. Ethiopia: number of reported cases of smallpox and numbers of vaccinations performed, 1971–1977

Zone	Estimated population (thousands)[a]	Number of cases						
		1971	1972	1973	1974	1975	1976	1977
North	4 017	1 751	760	20	30	0	0	0
Central	5 867	4 872	5 745	2 409	3 125	2 885	597	0
South-west	4 739	13 019	4 767	317	73	1	0	0
Shewa	5 565	1 884	1 065	1 034	320	524	0	0
South-east	6 915	4 803	4 662	1 634	891	525	318	0
Total	27 103	26 329	16 999	5 414	4 439	3 935	915	0
Number of vaccinations (thousands)		3 162	3 222	2 000	2 051	1 750	3 285	1 895

[a] See footnote[a], Table 21.7

were performed, nearly 15 times the number given during the preceding year; yet this figure represented no more than one-eighth of the population. It was clear that a long and difficult task lay ahead.

The Second Year, 1972

In 1972, more resources became available (Table 21.9). A staff which had grown to 67 by January 1972 rose to 82 by the end of the year as additional volunteers from Austria, Japan and the USA joined the programme. In November 1971, a special meeting was held with the provincial medical officers to explain the programme to them and to solicit their support. Gradually they, as well as staff attached to health centres, took an increasing interest in the programme and made substantial contributions. WHO assigned an additional epidemiologist—Dr G. P. Marchenko, who was transferred from the programme in Pakistan. A fleet of vehicles numbering 27 in January increased to 49 by the end of 1972, making the surveillance staff far more mobile. The transceivers, of which half were based at provincial capitals and the other half mounted on vehicles, greatly facilitated communication. Dr Weithaler and Dr de Quadros sought additional help wherever it could be found. Thus ensued, in successive years, a large number of cooperative undertakings with private and public sector groups, including the personnel of a leprosy control programme, mission groups, scientific expedition staff and emergency relief workers, all of whom were supplied with vaccine and asked to report cases of smallpox and to perform vaccinations. Volunteers were also found among visiting health professionals, a number of whom served the programme for many months without salary, receiving the same per diem as Ethiopian staff.

Major difficulties had, however, become more apparent. Only variola minor was found and mortality was low: in 1971, for example, only 530 deaths were recorded (a case-fatality rate of 2.1%). Even in the acute phase of illness, patients experienced so few symptoms that they were able to travel easily, spreading the disease to contacts. A second problem was widespread resistance to vaccination among the two ethnic groups, the Amhara and the Dorsey, which constituted most of the population of the central zone, northern Shewa and some adjoining areas. A third

Table 21.9. Ethiopia: staffing patterns, 1971–1979[a]

Category	1971	1972	1973	1974	1975	1976	1977	1978	1979
WHO advisers	2	5	4	7	16	25	5	4	4
Volunteers (from Austria, Japan and USA)	24	36	36	36	8	4	–	–	–
Ethiopian health officers and sanitarians	29	29	30	37	42	79	73	77	79
Ethiopian health staff (other)	–	–	–	–	–	111	173	170	193
Ethiopian staff—locally recruited	–	–	–	152	1 200	808	798	851	851
Clerical staff	9	9	9	9	12	15	30	34	34
Drivers and mechanics	3	3	3	–	–	30	37	47	43
Total	67	82	82	241	1 278	1 072	1 116	1 183	1 204

[a] Status as at end of each year.

problem was the widespread practice of variolation, to which, in 1971, more than 3000 cases (12% of the total) were attributed. Many more persons than this were known to have been variolated but, as was the practice in Afghanistan (see Chapter 14), only those who developed a generalized rash in addition to a lesion at the site of inoculation were counted as cases. Lastly, it had become apparent that such maps as were available were very incomplete and often erroneous. Accordingly, the teams found it necessary to prepare their own sketch maps of each *awraja* and its subdivisions, the *woredas*, in order to identify the locations of outbreaks.

By the summer of 1972, the control of smallpox had begun to improve. During the first 6 months of 1972, the number of reported cases had remained as high as in 1971, with one-third of the 538 *woredas* notifying cases. During the rainy season, the number of reported cases fell steeply, as it had in the same period of the previous year. Thereafter, the number of cases recorded monthly remained below 1000 despite an increasingly comprehensive surveillance system. The total number of cases reported in 1972 was 16 999—nearly 10 000 fewer than in 1971. Most of this decrease was accounted for by a sharply diminished incidence in the last 4 months of the year, 2363 cases being reported in this period compared with 10 725 in 1971. During 1972, 3.2 million additional persons were vaccinated.

Progress in the 4 provinces of the south-west zone was highly encouraging, although not unexpected because resources had been concentrated there. Containment vaccination throughout this zone had been extensive because of the widespread outbreaks and was readily accepted, indeed actively sought, by most of the population. There were, however, some tribal groups which caused difficulties. As was reported by some of the smallpox eradication staff, "... many workers were suffering at one time from human bites" (WHO/SE/72.48, Tilahun et al.). By the end of 1972, vaccinations equivalent in number to more than half the estimated population had been performed in the 4 provinces and the number of reported cases of smallpox in 1972 fell by nearly two-thirds. In 2 provinces, Ilubabor and Welega, transmission was interrupted by the end of the year.

A rapidly declining incidence in Eritrea and Tigray Provinces was most unexpected, however. These provinces, whose population was nearly as large as that of the 4 provinces in the south-west, had each been assigned only one sanitarian—Ato Tadesse Fissehaye and Ato Worku Gebre Selassie, respectively. Both were dedicated and imaginative workers and proved successful in overcoming extraordinarily difficult problems. Eritrea, although endowed with substantially more extensive health facilities, communications and roads than other provinces of Ethiopia, was torn by civil war. Large areas were periodically cut off so far as road travel was concerned, while other areas were completely inaccessible to government authorities. On assuming responsibility for the programme, Ato Tadesse Fissehaye, contacted all health units to establish a reporting network and to encourage them to vaccinate both patients and nearby inhabitants. As a native Eritrean, he was able to contact dissident groups to explain the programme and obtain their cooperation. Accordingly, he was usually able to travel throughout the province, despite the civil war, to investigate and contain outbreaks. He contained 65 outbreaks with 487 cases in 1971, and 10 outbreaks with 86 cases in 1972. The last endemic case in Eritrea occurred in December 1972. Only 2 importations, resulting in 3 cases, were subsequently discovered in 1973. Tigray, which was more mountainous and had fewer resources, presented a different type of problem. There, Ato Worku Gebre Selassie persuaded the able and widely respected governor to lend his per-

BY COURTESY OF D. A. HENDERSON, 1972

Plate 21.7. Smallpox staff in Addis Abeba, 1972. *Left to right:* James Lepkowski (a United States Peace Corps volunteer), Ashagre Hailemariam, D. A. Henderson, Tadesse Fissehaye, and Tarekegn Hailu.

sonal support to induce health and other civil authorities throughout the province to cooperate in a search for cases and their containment. Travel was not then hampered, and by the end of 1972 transmission had been interrupted in this province also. Importations were to occur in 1973 and 1974, resulting in 17 and 30 cases respectively, but both outbreaks were effectively contained. Except for these imported cases, the northern provinces remained free of smallpox after 1972. The early interruption of transmission in Eritrea and Tigray was fortunate because the intensity of civil strife in this area heightened significantly in later years, making it far more difficult to travel freely and to obtain the cooperation of the population.

A Year of Hope, 1973

In only 2 years the smallpox eradication staff, few though they were, had made remarkable progress, and the programme gained such momentum in 1973 that by the end of the year expectations were high that transmission might be interrupted within the next 12 months. The staff had become more experienced and, during twice-yearly seminar training programmes, had steadily modified and improved surveillance techniques. The staff at health centres were increasingly cooperative and participated more actively in reporting and in vaccination campaigns. In fact, 20% of all cases in 1972 were reported by the regular health services. Problems of transport and radio maintenance and repair were fewer, thanks to the Japanese volunteers; adequate supplies were available for camping and the arduous treks on foot or on muleback.

Surveillance methodology had been evaluated in June 1972 in an imaginative study which provided additional confidence in the approaches being adopted. A surveillance officer, Mr James Siemon, accompanied by a vaccinator, undertook a 14-day search in a remote mountainous *awraja* covering an area of 48 000 square kilometres and with a population of 275 000 (Quadros et al., 1973). No cases had been reported for 6 months. The 2-man team travelled extensively through the *awraja*, mainly on foot, making inquiries about smallpox cases among administrative officials and at the sole health centre and 4 health stations, at 8 schools, and at weekly markets. None of the administrative officials, village leaders or health staff knew of any cases. However, 5 different persons, at 3 markets and 2 schools, identified a single small outbreak of 8 cases in 3 households. Mr Siemon investigated the outbreak, which was 2–9 hours' walk from each informant, and discovered it to have been caused by an importation from another province. From follow-up surveys, it was confirmed to be the only outbreak then present in the whole *awraja*.

A description of surveillance activities as practised at this time is helpful to an understanding of the programme and how it functioned. In most provinces, 2 surveillance teams were assigned, each team being responsible for an area with a population of 500 000 to 2 million. The team leader prepared a sketch-map and drafted a rough tour plan so that each *awraja* could be visited regularly. In some provinces, this often meant a walking tour of 3 or 4 weeks in just one *awraja* as the team progressed from valley to valley. A team of 2 workers was found to be the most practical because its members could be more readily accommodated locally. For ease of travel, they carried minimal supplies but were given letters by administrative officials to local leaders requesting that they should be provided with food and accommodation. By staying overnight with local leaders, they became better acquainted with the local people and were often able to obtain assistance from them in searching for cases and performing vaccinations. As the programme gradually began to concentrate on the more mountainous central and northern areas, vehicles were less often used because travel by foot and by mule proved more practical and permitted access to more difficult areas. Accordingly, the vehicles available to the programme staff began to be used primarily for transporting teams and supplies to points accessible by road and picking them up again at an arranged rendezvous point after 2–4 weeks. On arrival in the *awraja*, the team visited the offices of the *awraja* and then the *woreda* administrators to inquire whether they were aware of smallpox cases. Because there was little contact between officials and villagers at that time, this procedure was rarely useful in finding cases. However, official letters from the *awraja* and *woreda* officials helped in making contact with village leaders. The team then visited each market, clinic, school and church. Weekly markets were a feature of both rural and urban Ethiopia, and although most of the people attending lived

within 3 hours' walking distance, some travelled for as long as 3 days. For market surveillance, careful planning of the tour was required because markets were held on different days in different villages. Clinics and schools were comparatively rare but, where present, they were often a helpful source of information. Coptic churches, a prominent feature of the mountainous plateau area, convened adults for Sunday services from distances of up to 15 kilometres. Other persons encountered on tour were also questioned about smallpox.

Because the population was sparsely settled, most of the team's time was devoted to travel. When groups were questioned about possible smallpox cases, vaccination was offered but no attempt was made to persuade those unwilling to be vaccinated or to vaccinate all persons in an area except where there was an outbreak. Outbreak containment consisted only in vaccinating those in geographical proximity. With so few staff, it was impossible for the team to remain at an outbreak site to ensure the isolation of the patient or the vaccination of absent contacts or of visitors who later came to the village. Not surprisingly, some outbreaks persisted for many weeks after the team's departure, and some resulted in the spread of smallpox to other villages.

During the first 6 months of 1973, an average of only 590 cases was discovered each month; 115 *woredas* reported cases—64 fewer than during the same period of 1972. With fewer cases and fewer outbreaks, surveillance staff were able to devote more time to search, and additional manpower could be concentrated in problem areas. From April to September the number of cases decreased steadily, reaching a low of only 71 cases in September. Areas known to be infected were few in number and widely scattered except in the central zone (Fig. 21.6).

In preparation for what was hoped might be the last smallpox season, an international seminar was convened in Addis Abeba at the end of the rainy period to which were invited representatives from the French Territory of the Afars and the Issas, Kenya and the Sudan. All these countries by this time were smallpox-free, the Sudan having been the last to eliminate the disease (at the end of 1972). Plans were coordinated for continuing surveillance along border areas and the possibility was explored for teams from these countries to undertake surveillance

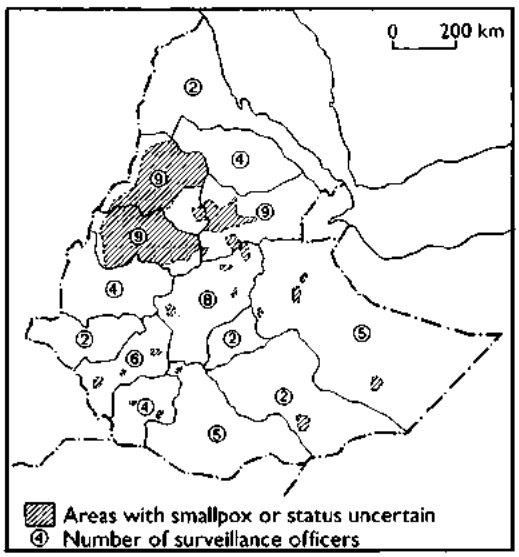

Fig. 21.6. Ethiopia: areas with endemic smallpox and number of surveillance agents assigned to each province, as of 30 September 1973.

programmes within Ethiopia in areas adjacent to their borders.

The remaining endemic areas, principally in Gojam, Gonder and Welo, were comparatively small but they posed enormous problems. The population was predominantly Amhara, many of whom adamantly refused vaccination despite the persuasive efforts of government leaders, village chiefs and priests. Meanwhile, variolation continued to be widely practised, performed by the heads of households when cases occurred in the vicinity. The terrain was the most mountainous and rugged in all of Africa and throughout much of the area security was a problem. In some areas, there was no government presence and smallpox eradication staff were forbidden to enter. It was apparent that helicopters would be invaluable for surveillance, but they were costly; appeals at this time to donor agencies as well as to the Ethiopian army met with no response.

To persuade villagers to accept vaccination sometimes required the teams to remain in an area for extended periods. The overcoming of resistance to vaccination required a somewhat different approach in each village. Some people accepted vaccination only if it was performed on the wrist (the site normally used for variolation); some would accept it only if it was administered by jet injector; in other areas, additional medications had to be

provided first. Not infrequently, weeks of inducement and cajoling were required to vaccinate even half the population of an infected village. Ethiopian and WHO staff showed unusual stamina, courage, imagination and persistence in solving the formidable array of problems, especially notable leadership being provided by 3 Ethiopian health officers—Ato Bono Hora, Ato Wassihun Woldetensie and Ato Zein Ahmed. Time and manpower were required, however, both of which were in short supply. Because of the special problems in these provinces, 2 additional WHO epidemiologists were recruited to permit the assignment of one to each of the 3 provinces, leaving 2 advisers to work with Ethiopian coordinators throughout the remaining 11.

In the autumn of 1973, an unforeseen disaster occurred. The eastern and north-eastern parts of Ethiopia experienced an extremely severe drought, followed by famine, during which an estimated 200 000 persons died. This was accompanied by an unprecedented migration of nomads into the highland areas and by a large-scale migration of the population from the endemic areas of Welo Province into other provinces. Many cases were imported into smallpox-free areas and into the neighbouring country of Somalia and the French Territory of the Afars and the Issas.

Because of the extensive movement of refugees, the number of cases increased to 542 in November and 508 in December, almost as many as had occurred during these same months in 1972. For the year as a whole, however, the 5414 recorded cases represented a decrease of nearly 70% from the 1972 figure of 16 999 cases. Ninety percent of the cases were from only 5 provinces, in which half the smallpox staff were concentrated. During 1973, 2 additional provinces, Gamo Gofa and Arsi, succeeded in interrupting transmission, bringing the number of smallpox-free provinces to 6. Much had been achieved, but it was becoming apparent that the eradication of smallpox from Gonder, Welo and especially Gojam was anything but a certainty. Resistance to vaccination in these areas was reflected by the proportion of the population that had been vaccinated. By the end of 1973, 8.3 million people in Ethiopia as a whole had been vaccinated, a total equivalent to one-third of the population, but in the central zone provinces, the corresponding proportion was only 20%.

A Year of Turmoil, 1974

The optimism and high expectations of early 1973 that a rapid interruption of transmission might be achieved had given way to the recognition that an arduous task lay ahead which would require the utmost persistence and imagination. Greater support from the government and the involvement of more Ethiopian staff were essential in order to cope effectively with uncooperative populations. Increased financial support from international sources was also required but was difficult to obtain. At this time, WHO considered the eradication of the severe variola major in Asia to be of higher priority, and such discretionary funds as were made available to the Organization had to be directed to the programmes in Bangladesh and India. Possible bilateral support for Ethiopia, meanwhile, remained in suspense as increasing civil strife began to envelop a country beset with economic crises, famine and rebellion against the traditional feudal system of government.

The programme's resources were primarily concentrated in the central zone provinces but the working conditions there became increasingly difficult. Because of armed conflict, *woredas* and sometimes entire *awrajas* were declared by the army to be too dangerous to permit work to continue. In other areas, the teams had to travel with a security escort. In Welo and the south-east, in which outbreaks accompanied refugees, the teams sought and obtained assistance in reporting and vaccination from relief workers distributing food supplies.

Special assistance to the programme was provided during the early months of 1974 by health staff from the French Territory of the Afars and the Issas, Kenya and the Sudan in an exceptional display of international cooperation. It was beyond Ethiopia's capacity to contend successfully with the outbreaks among nomads and refugees in the huge eastern desert areas. Here, with the full approval of Ethiopia, the authorities of the French Territory of the Afars and the Issas responded by providing 5 teams, comprising 46 persons supported by 20 vehicles and 3 helicopters for a 6-week programme of search and vaccination. This operation extended up to 300 kilometres inside the Ethiopian border in the eastern part of Welo and Hararge. To support the effort, Ethiopian staff established petrol depots at key points and accompanied

The Sudanese Search in Western Gojam Province

Search and vaccination in the difficult area of western Gojam Province were undertaken by a Sudanese team in a journey characterized by great ingenuity and determination. Travelling in 3 Land Rovers, 12 persons required 2 months to traverse some 250 kilometres through Gojam Province from the Sudanese border to the town of Bahir Dar in Ethiopia. Led by a Sudanese sanitarian, Mr Abdul Gadir El Sid, the team had to carry with it all the petrol and most of the supplies needed. Sudanese pounds were acceptable currency for the purchase of food over half the distance; for the last part of the journey, the team members needed Ethiopian dollars, and to obtain them they sold a supply of blankets which they had brought with them just for this purpose. The "roads" over which they travelled had not been traversed for years. It was necessary for them to construct bridges and in many areas to walk ahead of the vehicles, clearing a path with large knives. In some places, the underbrush was so dense that it had to be burnt (on one occasion the flames nearly consumed one of the vehicles). Mechanical breakdowns, poisonous snakes, wild animals and insects were daily problems. Nevertheless, they persisted in their journey, during which they contacted and vaccinated some 20 000 people but found no smallpox. They were gratefully received in Bahir Dar by Ethiopian staff, provided with Ethiopian dollars and, after a brief rest, returned home by the same route.

the French teams, coordinating the overall work through the transceiver network. Meanwhile, a Sudanese team of 12 persons with 3 vehicles undertook a 2-month programme of search and vaccination throughout the western third of the difficult Gojam Province. In the south, Kenyan teams began a continuing programme of search and vaccination in Ethiopian *awrajas* adjacent to Kenya.

Every possible effort was being made to augment the capacity of the programme through cooperative work with the regular health services staff, relief workers and others. Even the malaria eradication staff began to participate after several cases of smallpox had occurred among the malaria workers themselves. The coordination of such disparate groups and activities was difficult, however; it became even more so when, because of the intensifying civil war, a number of foreign volunteers left the programme. Ethiopian health officers and sanitarians served to fill the gap, their efforts being augmented by students who were hired as temporary staff during an extended holiday from the university, which was closed owing to the civil unrest.

Despite the chaos and obstacles, progress continued to be made. Transmission was interrupted in April in Kefa Province, leaving the entire south-west zone smallpox-free. In the northern zone provinces of Eritrea and Tigray, only one importation occurred and this was contained. In the south-east zone, the outbreaks were contained in the populous areas of northern Hararge by mid-year. Smallpox continued to spread among desert nomads, but few of the staff believed that transmission could be long sustained in this sparsely settled area. Gonder, Gojam and Welo remained the principal areas of concern.

More resources were required for the central zone provinces and, in June, came the welcome announcement that the Surgeon General of the United States Public Health Service had arranged to make available US$220 000 from his domestic health budget allocation specifically for the lease of 2 helicopters. Planning began immediately to mount a special search programme, to commence in late 1974, as soon as the helicopters, pilots and mechanics had arrived. A Canadian company, under contract to WHO, arranged to fly the helicopters to Ethiopia and recruited Canadian pilots and mechanics, under the leadership of Mr Robert Lavack and Mr William Waugh. Meanwhile, it was decided to make intensive efforts to continue the programme throughout the rural areas despite the difficulties of travel created by the advent of the rainy season.

The challenge of keeping the programme in operation was already enormous, but in 1974 the situation was exacerbated by the beginning of a major revolution. The Emperor was deposed and a new government with a different administrative structure began to take shape. An important tenet of the

The Death of Dr Petrus Aswin Koswara

The emotional and physical strain associated with field work in Ethiopia was especially great in 1974; it cost the life of one WHO smallpox eradication programme adviser, Dr Petrus Aswin Koswara. He was the only WHO adviser to die while actively engaged in the programme. After serving brilliantly as the director of the successful programme in Indonesia, Dr Koswara joined the Ethiopian programme in 1972. In 1974, he was working in Welo Province, where he was responsible for the planning and logistics associated with the new helicopter-assisted search programme. On returning from Welo one afternoon after weeks of exhausting strenuous field work, he experienced severe chest pain and died that night of a heart attack. He was only 43 years old. His wife and their two children returned to Jakarta, where Dr Koswara was buried. He was decorated posthumously by the President of Indonesia and given a state funeral.

new government was the abolition of the feudal system of land tenure, an action welcomed in most areas but forcefully resisted in others. At the same time, the long-standing revolt in Eritrea intensified; violence increased among the Amharic peoples of the central zone; and the traditional antagonisms between Ethiopians and ethnic Somalis throughout the Ethiopian portion of the Ogaden desert erupted into sporadic open warfare as armaments began to be supplied to guerrilla forces calling themselves the Western Somalia Liberation Front. These problems persisted over the succeeding years, never completely subsiding. Some of those engaged in hostilities were supportive of the smallpox eradication programme and arranged for the staff to work in areas otherwise inaccessible to government authorities. Others, however, attacked smallpox eradication teams, kidnapped some of them, and on one occasion killed 2 of the Ethiopian vaccinators. Nevertheless, programme staff continued their work, both Ethiopian and international workers often serving in areas in which no other government staff could operate.

The special campaign employing helicopters began, as planned, in mid-November 1974 with the object of searching the more inaccessible highland areas. This took careful preparation as fuel depots had to be established and a scheduled programme of search elaborated for areas of which existing maps, at best, only approximately represented the actual terrain. Camping equipment and food were also necessary because supplies in the drought-stricken areas were scarce. The helicopters, operating from base camps, ferried teams into the most difficult and remote areas.

Plate 21.8. P. A. Koswara (1931–1974) seated (*centre*) with 2 Ethiopian colleagues, Endale Alemayehu and Tedla Tegegn, shortly before his death.

Thereafter, the teams proceeded by foot and on mules to an arranged pick-up point over a period of 7–10 days. The helicopters provided logistic support and were used to transport staff to confirm rumours of outbreaks. The teams searched for cases and performed vaccinations. Where resistance to vaccination was encountered, administrative officials were flown in to help to persuade the villagers. As these operations progressed, the staff were surprised to find that, in many areas, resistance to vaccination was less of a problem than it had been before. This phenomenon was attributed in part to the dramatic appearance of teams by helicopter.

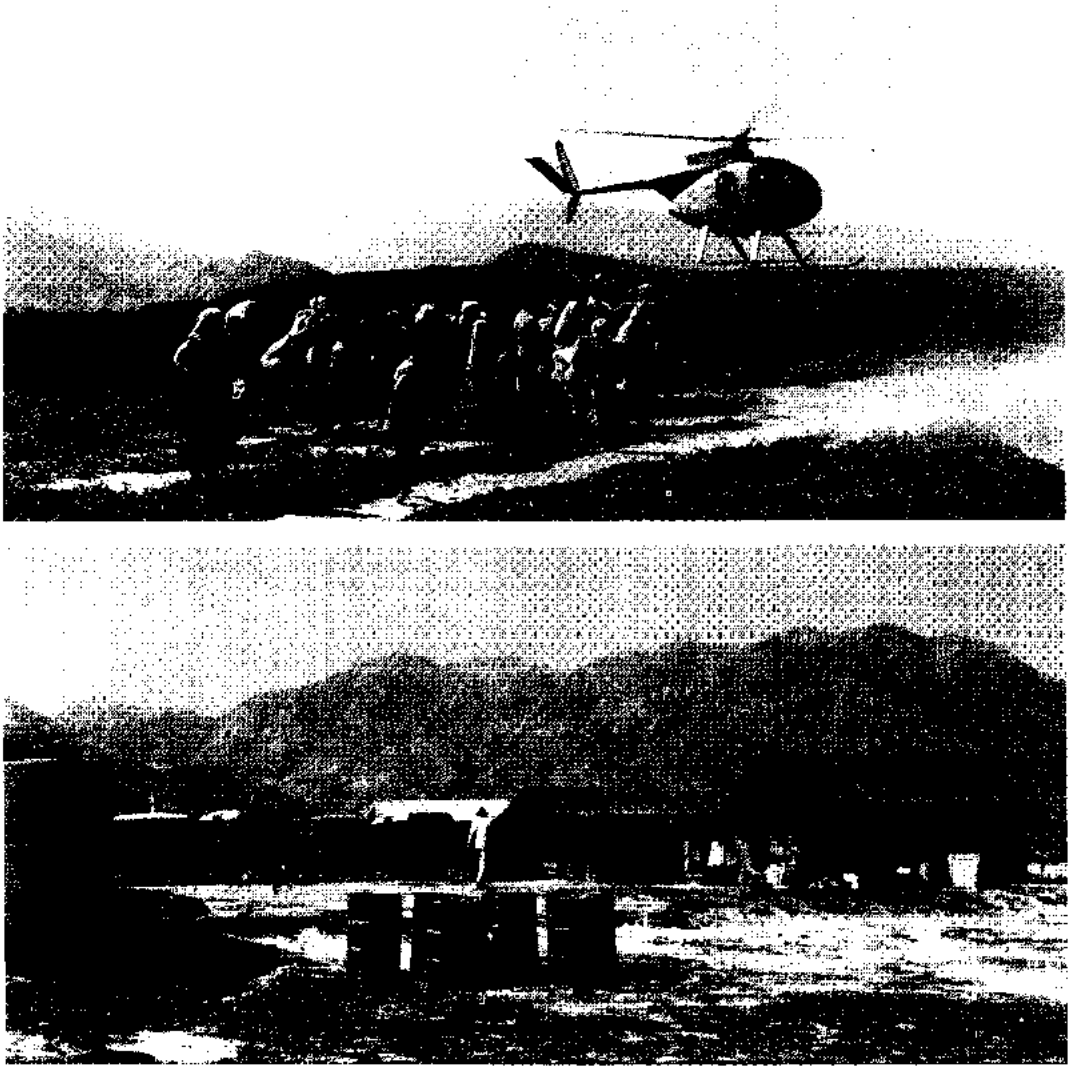

Plate 21.9. **A:** Helicopters were used in the Ethiopian programme from 1974 for smallpox searches in inaccessible areas. Although they could carry 4 passengers at sea level, they could not transport more than 3 persons at the high altitudes of the vast central mountainous area. **B:** The limited flight range made it necessary to establish depots of fuel drums in camps.

The helicopters greatly facilitated efforts but an operation such as this was costly and was attended by other problems. One hour of flying cost about US$250 and thus careful planning of use was mandatory. Moreover, the 4-passenger helicopters did not have a great range and at the high altitudes of the central plateau could not transport heavy loads. Thus, fuel depots had to be carefully sited and accessible by the heavy trucks required to transport the drums of fuel from Addis Abeba. Serious delays in the schedule occurred when helicopters experienced mechanical failures or other events took place. Such incidents included the destruction of one helicopter by a hand grenade shortly after a team's arrival in a village; a second was hit by a bullet which penetrated the fuel line, causing a fire and a forced landing. On another occasion, a helicopter lost its bearings, made a forced landing when fuel ran out, and was not found for 2 days. And on yet another occasion some years later, rebel forces captured a helicopter and pilot and held them to ransom (Plate 21.10). Although nobody was injured or killed as a result of these incidents, some of the pilots returned home within days of arriving in Ethiopia. Most

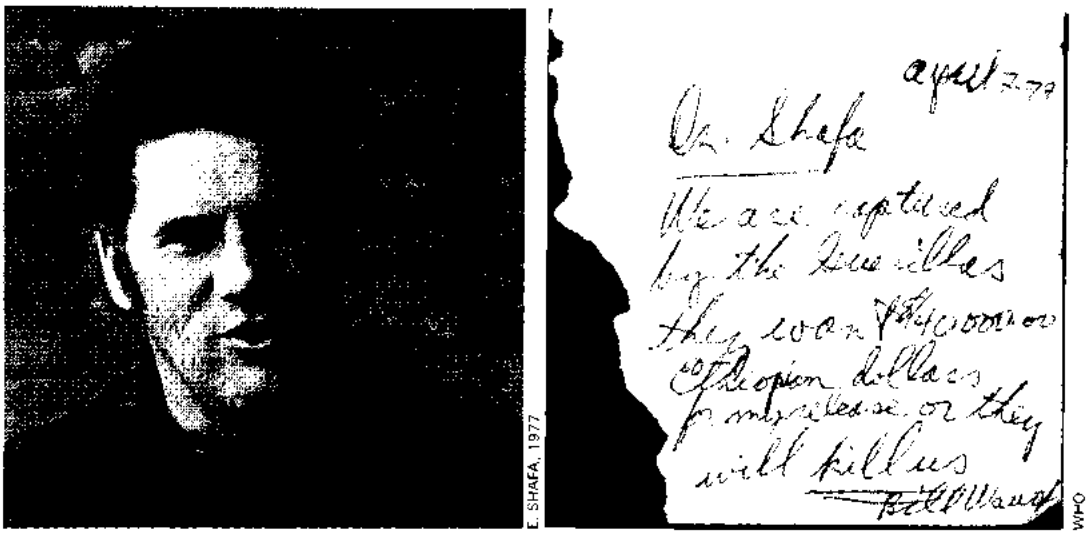

Plate 21.10. William Waugh, a Canadian helicopter pilot, was captured in 1977. He managed to send this message to Ehsan Shafa, of the Smallpox Eradication unit at WHO Headquarters, who was in Ethiopia. It reads: "April 7–77 Dr. Shafa We are captured by the Guerillas they want $40 000.00 Ethiopian dollars for my release or they will kill us, Bill Waugh". He was released 4 days later when this picture was taken, without the ransom having been paid.

were undaunted and became as expert in the diagnosis of smallpox and the strategy of the programme as the senior programme staff.

The helicopter-supported operation detected fewer smallpox outbreaks than had been expected; most of those discovered were rapidly contained. In Gonder, few cases were found and by December the persistent focus in one *awraja*, which was responsible for 60% of cases in the area, had been eliminated, leaving only one seriously affected *awraja*. In Welo, fewer smallpox cases were discovered in the northern area than had been expected, although continuing transmission in the south remained a problem. In Gojam, by the end of the year, smallpox appeared to be limited to only 24 of the province's 1800 *debers*.

By the end of 1974, 4439 cases had been discovered, 20% fewer than during the previous year; the number of provinces in which transmission had been interrupted had risen from 6 to 8 as both Kefa and Sidamo in south-western Ethiopia became smallpox-free. Search continued in both of these provinces but the few cases that were found could be identified as importations and were quickly contained.

The Final Phase, 1975–1976

At the beginning of 1975, with mounting civil disorder and with increasingly large areas in the endemic provinces inaccessible to the programme staff for long periods of time, it seemed more and more questionable whether adequate resources could be deployed sufficiently quickly and effectively to interrupt transmission. In fact, it seemed possible that the degree of control that had been achieved was at risk of being lost, which would permit smallpox to spread widely through Ethiopia and into other countries. If additional resources were to be made available, however, they would have to be drawn from other programmes. But eradication of the severe variola major in Asia continued to have priority, and although excellent progress was being made in India and Nepal, in the early months of 1975 Bangladesh experienced major epidemics (see Chapter 16) associated with famine and extensive movements of refugees. Not until the summer of 1975 was it reasonably certain that smallpox could be eliminated from Asia. When smallpox transmission was interrupted in India in May 1975 and in Bangladesh a few months later, it was possible to divert resources and energies to Ethiopia—then the world's last remaining country with smallpox. At this favourable turn of events, Ethiopian and international staff alike renewed their endeavours to attain what had once seemed such a distant target—"Smallpox Zero".

Surveillance of Smallpox in a Hostile Area

A special problem faced by the smallpox eradication staff was surveillance among a population living in the Blue Nile gorge, a ravine which formed the southern border of Gojam and was one of the widest and deepest in the world. At least 2 days were required to travel from one edge of the gorge to the other. Large numbers of people inhabiting the gorge were hostile to the intrusion of strangers; when the teams visited, they often had to be accompanied by armed security forces. During much of 1974–1975, the teams were unable to enter the gorge at all and thus were limited to conducting surveillance–vaccination activities around its rim. On one occasion, rumours were received about the existence of smallpox in one of the villages, whose inhabitants were thought to have been responsible for killing the members of a German Blue Nile expedition. A young schoolboy who was a native of the area and had relatives in the village volunteered to investigate. He went to the village and, while playing with other children, succeeded in obtaining scabs from a child who had experienced a disease with rash. Laboratory investigation confirmed it to be smallpox.

It was not until 1977 that the fighting subsided sufficiently to permit search teams, accompanied by civil guards, to travel widely through this area. Fortunately, transmission had ceased by then even though few persons had been vaccinated.

Throughout the summer of 1975, the staff, still numbering less than 100, continued the struggle with smallpox in the highlands of the central zone and adjacent areas of Shewa, as well as in the Ogaden desert area of Hararge (Fig. 21.7). Unexpectedly, additional manpower became available when the authorities decided to send 60 000 students into villages throughout the country in a special campaign to improve literacy. The government agreed that some could also work with the smallpox eradication teams, and thus many were trained in techniques of case search and vaccination. The students proved to be especially valuable, since they were natives of the area in which they were working and could both identify persons with political influence and induce the villagers to accept vaccination.

Progress in Asia eventually came to be measured in terms of the number of currently "active outbreaks" in a village or sector of a town—i.e., those in which a case had occurred during the preceding 6 weeks. This system of measurement was introduced into the Ethiopian programme in 1975 but it was difficult to apply. An epidemiologist was required to revisit the site of an outbreak after 6 weeks to confirm that transmission had ceased and that the site could be removed from the list of "active outbreaks". Because of the paucity of staff and the periodic prohibitions on travel in large areas, such visits were sometimes unavoidably delayed. Moreover, it

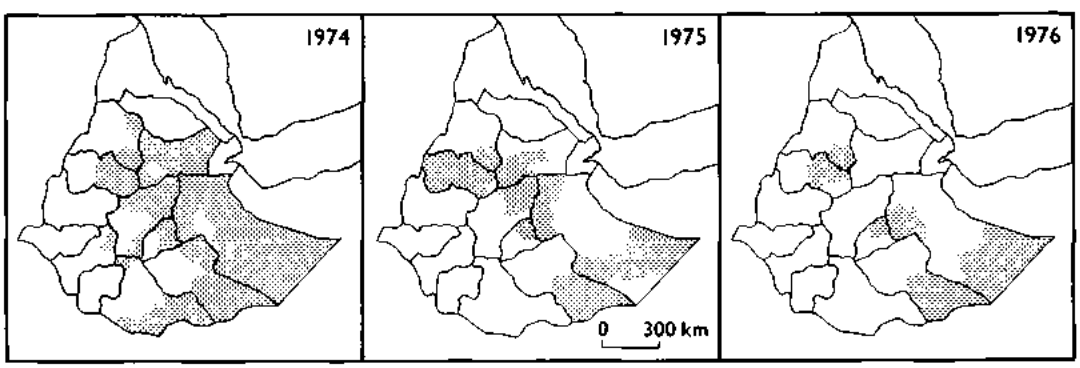

Fig. 21.7. Ethiopia: *Awraja* areas (shaded) in which cases of smallpox were reported, 1974–1976.

was no easy matter to deal with an Ethiopian "village", a collection of houses often dispersed over many square kilometres. Nevertheless, the staff began to define the smallpox problem in this way and by mid-year had evolved a reasonably effective data collection system. By the end of July 1975, there were only 131 known active outbreaks occurring in 13 clusters. The clusters were spread over about 15 360 square kilometres, little more than 1% of the country's total area (Table 21.10). Many of the outbreaks in Gojam, Shewa and Gonder, however, had occurred in areas which the teams had been forced to leave because of civil strife, thus precluding their removal from the list of active outbreaks.

As civil disorder was so widespread, some enbassies decided that effective work in the countryside was impossible and too dangerous and so terminated the assistance of their countries; the remaining volunteers from Austria and the USA were withdrawn, although those from Japan continued to work. The smallpox eradication staff, however, believed that they might yet be successful if conditions did not deteriorate further. In fact, the problems became more acute. Petrol for vehicles, which had been in short supply, was brought to the capital by truck in an armed convoy from the coast. In June, because of the destruction of a major road bridge, the supply line was interrupted and rationing was imposed in Addis Abeba. In many parts of the country, no petrol at all was available. However, the Acting Resident Representative of the United Nations Development Programme, Mr John Phillips, who in 1971–1972 had been instrumental in initiating the smallpox programme in Botswana (see Chapter 20), worked out an imaginative scheme with the French government and an oil company to ship petrol by train from the city of Djibouti to Addis Abeba.

Table 21.10. Ethiopia: status of smallpox as at 23 July 1975

Regions	Number of clusters	Number of active outbreaks	Approximate area (km²)
Hararge	3	6	2 517
Shewa	1	24	3 600
Welo	2	6	234
Gonder	2	15	2 450
Gojam	4	79	6 550
Bale	1	1	9
Total	13	131	15 360

From there it was distributed to the regions by truck and by a chartered DC-3 fixed-wing aircraft. Fortunately, there remained a large residual stockpile of aviation fuel in Addis Abeba which the government made available to the programme, thus permitting continued helicopter operations.

In July 1975, Henderson held meetings with Ethiopian and WHO staff to plan an intensified programme extending to the end of 1976. It was hoped to utilize monetary contributions from Canada, the Netherlands and the USA, vaccine from the USSR and additional support from the WHO regular budget. The revolutionary government agreed to issue a proclamation declaring the programme to be of the highest priority. The new plan provided for 85 Ethiopian surveillance officers, 16 WHO advisers and as many as 1200 temporary field staff; the number of helicopters was increased from 2 to 4; additional vehicles and considerable quantities of camping equipment were also provided.

In October, more ample facilities were made available for the programme's headquarters, including an automotive repair shop. At the end of the year, an exceptionally able Ethiopian health officer, Ato Yemane Tekeste, was named director of the programme; Dr Weithaler continued to serve as its senior WHO adviser.

Activities steadily intensified, especially in the highland plateau areas, to which the most able Ethiopian and WHO staff were assigned. With additional locally recruited staff available, it became possible to assign teams to search for cases more widely and more frequently and to remain in outbreak areas until transmission had ceased. However, areas in which organized operations could not be undertaken because of the lack of security continued to be a problem. In many of these areas, locally recruited staff who were known to the dissidents opposing the government were sometimes able to travel quite extensively to search for cases and to vaccinate, although not without risk. It was during this period, in Gojam, that one worker was killed and a second captured and presumably killed by dissident groups.

By the end of 1975, smallpox transmission had been interrupted in 2 more regions, Shewa and Welo. No cases were detected in Gonder between July and December 1975, but because of the extent of the areas that could not be searched, the staff remained

uncertain as to the true situation in the province. The main problem was presented by Gojam, in which 4 contiguous *woredas* in and adjacent to the Blue Nile gorge, all heavily infected, could not be entered, and from this source cases were repeatedly exported to other areas. The teams sought to contain this focus through the surveillance and vaccination of the population of adjoining areas, but many individuals resisted vaccination.

The other principal focus of smallpox was in the vast Ogaden desert. Smallpox among the nomads had spread slowly but steadily from the highlands of the north-west into the Ogaden desert area of south-eastern Hararge, with occasional spread into Bale and Arsi Regions. From the initial reports of smallpox eradication staff in the area, there appeared to be few problems in containing this focus. They guessed that the affected population was not more than 300 000, of whom a third lived along a river, readily accessible by vehicle. As a result of the vaccination of people settled along the river, of refugees receiving food at shelters, of nomads when they stopped at water-holes and of other individuals contacted during search operations, the WHO epidemiologist estimated that at least 60% of the population had been protected. In a population so sparse and scattered, and so well vaccinated as this, everyone agreed that continuing transmission should cease quickly. However, the possible spread of smallpox into the part of the Ogaden desert that lay within Somalia was also a source of concern. Accordingly, periodic border meetings were arranged between Ethiopian and Somali staff. The Somali programme director reported at one of these border meetings in August 1975 that 85% of the nomads in Somalia had been vaccinated and assured everyone that surveillance in Somalia was most thorough. Only much later did it become evident that both Somali and Ethiopian staff assigned to the Ogaden area had greatly overestimated their achievements and underestimated the size of the population and the severity of the problem.

The early months of 1976 were characterized by far more intensive efforts but increasing organizational turmoil. The arrival of additional WHO epidemiologists and the acquisition of more vehicles, 2 more helicopters and a small fixed-wing aircraft, as well as the employment of many more local staff, overtaxed the capacity of the administrative structure. The helicopters began to be scheduled for as many as 8–10 flying hours a day, which exceeded safety limits and created difficulties in providing the requisite maintenance. Close field supervision of the increased staff became more difficult; the provision of field supplies was increasingly delayed; and the effective management of funds for the field payment of temporary staff and the purchase of supplies deteriorated. On a field visit in late February 1976, Henderson found a well-organized operation in progress throughout Gojam, Welo and Gonder under the overall supervision of Dr de Quadros and directed at regional level, respectively, by Ato Bono Hora and the WHO epidemiologists, Dr P. R. Arbani from Indonesia and Mr Gary Urquhart from the USA. In other areas the situation was less satisfactory. In northern Hararge, Henderson discovered that 5 outbreaks of chickenpox had been misdiagnosed as smallpox by inexperienced field staff. The most disturbing observations were made in the Ogaden, where supervision and organization were seriously deficient. At a watering-place only 20 kilometres from the Somali border, a smallpox isolation hut, located in the middle of a nomad camp, had no watchguard and was frequently visited by people from the camp; many unvaccinated persons were found in the area. At another camp, 2 individuals were encountered who had been

E. SHAFA, c. 1975

Plate 21.11. Poerwokoesoemo R. Arbani (b. 1941) was a WHO epidemiologist in Ethiopia, 1975–1979, having previously served in the same capacity in Pakistan since 1973. Before that, he had played an active role in the eradication of smallpox from Indonesia.

infected in the office of the camp physician by patients summoned for examination from the smallpox isolation facility. It was apparent that the optimism of the field staff in the Ogaden was unfounded.

The management of the programme was reorganized on 5 March 1976, and from then on rapid progress was made. A special task force for the endemic regions was created, with Ato Yemane Tekeste as programme director, Dr de Quadros as chairman, Mr Lavack as director of helicopter support operations, and Mr John Copland, administrative officer for smallpox at WHO Headquarters, as finance officer. Dr Weithaler was assigned to coordinate activities in the non-endemic areas; Ato Tesfaye Temelso and the WHO epidemiologist Dr Bert van Ramshorst assumed responsibility, under the direction of the task force, for operations in the Ogaden.

The tempo of activities increased in 1976 as both government authorities and WHO staff sought desperately to contain the world's only remaining focus of smallpox. It was possible to employ additional local staff through the use of funds made available by a special contribution from the USA of US$3 million in May of that year. New outbreaks continued to occur, however, until August (Fig. 21.8). The focus in Gojam was eventually contained by using armed civil guards who accompanied teams moving through the area; the last case occurred at the end of March. In Gonder, however, in January, after nearly 6 months without any cases having been detected, search teams were able to penetrate an *awraja* in the Blue Nile gorge which had been inaccessible for nearly a year, but in which fighting had recently diminished. There the teams discovered that smallpox had continued to spread (Table 21.11). Although this focus was near the outbreak area in Gojam, the two were unrelated. An intensive surveillance–containment programme was conducted, again employing civil guards, but transmission was stopped only with difficulty. As the search was extended around this area, another focus of 24 outbreaks with 140 cases was discovered 120 kilometres to the north. An itinerant musician had introduced the disease in December 1975 from the Blue Nile gorge. Fortunately, the population in the infected area proved to be receptive to vaccination, and on 29 June the last outbreak in the central zone provinces was discovered and contained.

Meanwhile in the Ogaden desert areas of Hararge and Bale, smallpox outbreaks continued to occur among the nomads, but the sources could rarely be traced because of the frequent movements of the different nomadic bands. Additional resources were deployed there in March and a better organized, more systematic pattern of search was developed employing more than 200 locally recruited staff.

In addition to helicopters, fixed-wing aircraft were chartered by WHO, and others were provided by the Netherlands and the Norwegian Save the Children Foundation. Search activities were compromised by sporadic fighting and the occasional kidnapping of staff and WHO advisers, who were taken to Somalia but eventually released through the intervention of United Nations officials. In addition, during this period 9 of the programme's vehicles were seized and taken across the border. The Somali guerrilla forces sometimes hampered operations, but more often than not took steps to protect the teams. In one town, to which a team had been brought by helicopter, notice was given by guerrilla forces that an attack had been planned and that the team should leave. As the helicopter took off, fighting immediately broke out. On other occasions, guerrilla forces attacked government buildings, killing the occupants, but did not molest the personnel of

BY COURTESY OF Y. TEKESTE, 1978

Plate 21.12. Yemane Tekeste (b. 1944), the director of the Ethiopian smallpox eradication programme, 1976–1979, checking the vaccination scar of a chickenpox patient in Gamo Gofa Region.

smallpox camps in the same town. For Ethiopian and WHO staff alike, working in the Ogaden was a trying experience. Many participated in the operation but special credit must go to the dedicated Ethiopian staff, to the helicopter pilots, and to Ato Tesfaye Temelso, Dr van Ramshorst (Netherlands), Dr do Amaral (Brazil), Dr M. N. El Naggar (Egypt), Dr Alexander Gromyko (USSR), Mr Carl Hasselblad (USA) and Dr J.-P. Ryst (France).

Gradually, it became apparent that in the Ogaden desert, smallpox was persisting primarily as a result of transmission back and forth between desert nomads and agriculturalists settled along the Shebele river, which divided Hararge and Bale. Efforts to control the spread, however, were severely hampered in the summer by the most serious flood in decades, which destroyed roads and river crossings and displaced numerous villagers. Across the river in the southern half of Bale, fighting between Ethiopian and guerrilla forces had greatly intensified and not until the middle of July was it possible for teams to enter this area. On 22 July, one of the teams discovered an outbreak in the small nomad village of Dimo in Bale, the first case having occurred on 5 June. Containment vaccination was immediately

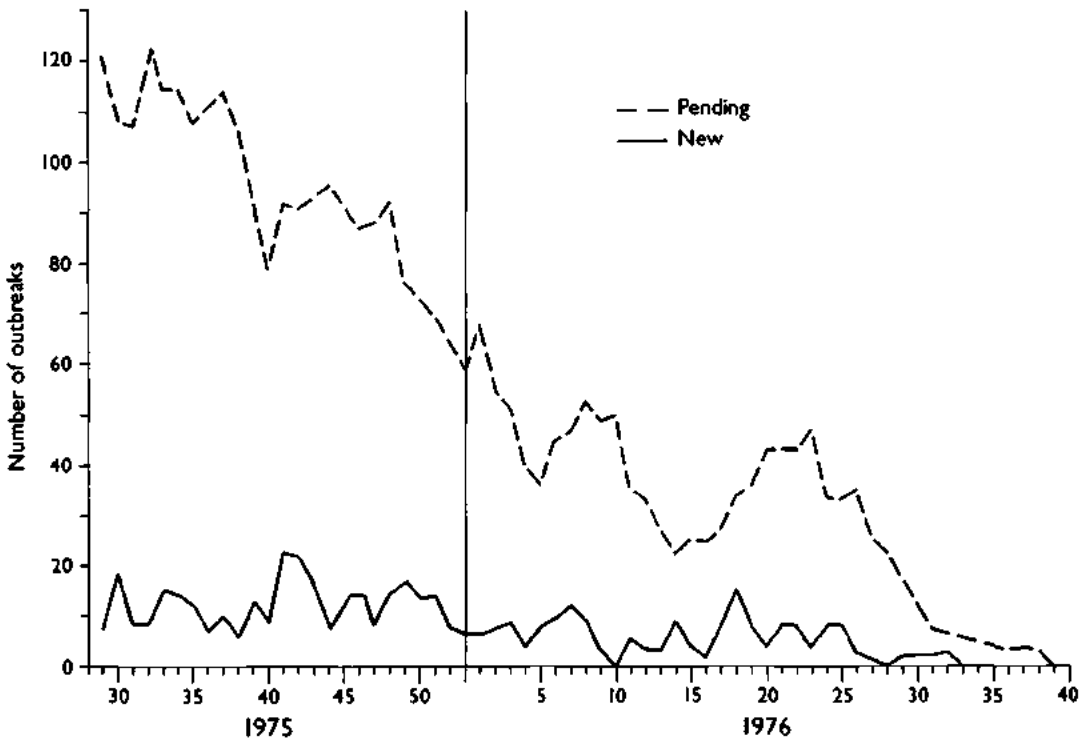

Fig. 21.8. Ethiopia: number of outbreaks pending and newly detected, by week, 1975–1976.

Table 21.11. Ethiopia: number of active outbreaks at month's end, January–September 1976

Zone/region	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.
CENTRAL									
Gojam	15	13	4	1	0	0	0	0	0
Gonder	11	18	15	16	33	21	4	1	0
SHEWA	1	0	0	0	0	0	0	0	0
SOUTH-EAST									
Arsi	1	0	0	0	0	0	0	0	0
Bale	0	2	1	0	2	0	2	4	0
Hararge	14	19	7	10	8	14	4	0	0
Total	42	52	27	27	43	35	10	5	0

A Missing Team—Chronology of Events

Work in the Ogaden was difficult enough. Guerrilla forces made it even more problematic.

Events as experienced by Ethiopian staff:

4 June 1977

Early morning—Surveillance Officer Ato Metiku reported to Addis Abeba by radio from Warder (a town in the Ogaden) that the WHO epidemiologist Dr Claudio do Amaral and a team comprising an assistant surveillance officer, 2 interpreters and a driver had not returned as expected on the previous evening. They had gone by Land Rover some 120 kilometres away to check on a rumoured smallpox case.

07.00 hours—The helicopter with Ato Metiku searched without success and returned to base.

10.00 hours—A fixed-wing aircraft joined in a second unsuccessful search.

15.00 hours—The two planes began a third search and at 17.50 hours, the vehicle was sighted. Because dusk had fallen it was decided to send the helicopter the following morning.

5 June 1977

06.00 hours—The helicopter flew to the site and many people were seen gathered around the vehicle waving white cloths. Fearing gunfire, the helicopter had to remain at a distance. From there, no team members could be identified.

12.00 hours—The helicopter returned to the site; this time a truck was observed parked next to the vehicle, again with many people surrounding it but no one waving.

15.00 hours—Two locally recruited Ethiopian staff volunteered to be dropped near the site (about 3 kilometres away) to obtain information. Special signals were arranged for them to identify themselves to the helicopter, which would keep watch from a distance and pick them up on 6 June at a site 30 kilometres away, on signal.

16.00 hours—The helicopter returned to the site but the vehicle was gone and the volunteers could not be seen. On returning to base, the truck seen previously was spotted. As the helicopter flew closer 2 individuals jumped from the truck and began firing at it.

Evening—At a special meeting, it was decided to bring in a second helicopter for search; 2 additional Ethiopian staff volunteered to be dropped at the site on the following morning hoping to learn something of the fate of their colleagues and of the team.

6 June 1977

07.30 hours—The volunteers were dropped at the site; helicopter search continued over a widening area.

14.00 hours—A flight over the original area revealed no sign of the volunteers.

16.00 hours—The helicopters flew to the pick-up site; one volunteer was seen but did not signal. The pilot returned to base at 19.15 hours.

Evening—Ato Metiku arranged in secret with the town-dwellers' association for a group of villagers to walk to the site.

7 June 1977

It was decided that all the aircraft should undertake a final area-wide search and then await instructions. Arrangements were made for a DC-3 fixed-wing aircraft to fly additional fuel to the area. The volunteers were located and retrieved by the helicopter; they had been unable to obtain any information.

8 June 1977

The Director-General of WHO sent a telex from Geneva to the Minister of Health of Somalia requesting assistance from the Somali border guards. Daily telex and telephone contact was established by Geneva with Addis Abeba and Mogadishu.

9 June 1977

A surveillance officer from Warder reported that a villager had told him that he had seen Dr do Amaral and the team on 6 June being taken by guerrilla forces to Deghbur, another area in the Ogaden.

Ato Yemane Tekeste and another high-ranking Ethiopian official left for Deghbur to be available to participate in negotiations should the captors make contact with the government.

11 June 1977

A telex was received in Geneva from the WHO Representative in Mogadishu with the message that the team was in Hargeisa, Somalia.

Events as related by Dr Claudio do Amaral:

3 June 1977

We left Warder at 07.00 hours to investigate a rumoured smallpox case 120 kilometres to the north. About 80 kilometres from Warder, 2 men with sub-machine-guns started shooting at us and ordered us to stop. Within minutes, they were joined by many others who ordered us out of the car, took everything we had and made us lie on our backs with our arms up. At that moment, I thought it was the last day of my life! Suddenly, one of their leaders appeared and took us to a village 300 metres from where we had been captured. He identified the group as being soldiers of the Western Somalia Liberation Front. We talked about the smallpox eradication programme and what we were doing, but he said that we had no right to be in the area, and emphasized that they could release us or kill us as they chose. We were given Somali dress and provided with goat meat and camel milk. We slept that night in the open air guarded by 2 men with sub-machine-guns.

4 June 1977

At about 15.00 or 16.00 hours we heard the helicopter and saw the fixed-wing plane but I hid, fearing they might land and be captured. That night we slept in the same place.

5 June 1977

In the morning, we again saw the helicopter and with a gun at my head, I was told to contact the pilot by radio to request him to land. I convinced our captors, however, that radio contact was not possible. The leader then ordered me to take off my shirt so that they would see my white skin and be persuaded to land. Again, I refused, persuading him that the pilot could not recognize colour from such a great distance. Fortunately, neither plane tried to land. Surprisingly, in the late afternoon, a vaccinator appeared who was from the village to which we had intended to go. He reported that the case we had intended to see was chickenpox, not smallpox! We were then driven to another village, where, we were told, we should be informed as to what would be done with us.

8 June 1977

After 2 days when nothing appeared to be happening, we were driven to yet another village, 120 kilometres further away, where we met a more senior leader. Once again, I showed my passport, explained I was Brazilian and described the smallpox eradication programme. To my great surprise, he knew all about our movements as well as the names of all the epidemiologists and where they were stationed. The leader said they would hand us over to the Somali authorities. That night they gave us a small hut and blankets for sleeping.

11 June 1977

We were handed over to the National Somalia Security authorities and arrangements were made for me to fly to Mogadishu on 18 June and to Addis Abeba on 22 June. The vehicle, after repair, was to be returned to Ethiopia.

instituted. In all, 16 cases occurred, 9 of the persons concerned having been variolated. The Dimo outbreak proved to be the last in Ethiopia, (Table 21.11) and for many weeks it was thought to have harboured the world's last case of smallpox—that of a 3-year-old girl who had become ill on 9 August. She had been variolated as well as vaccinated during the incubation period of the disease.

Active search continued and intensified throughout the country, on the assumption that in a country so large and with so many inaccessible areas, smallpox must be present somewhere. In many areas, especially in the south, the task of search was greatly facilitated by the new farmers' cooperatives and urban dwellers' associations. Through contact with the leaders of such organizations, it was possible to explain the objectives of the programme and to enlist the assistance of the population in reporting suspected cases. To encourage such reports, a reward was offered, a practice first initiated in January 1975 in Gonder.

Surprisingly, week after week passed with no additional smallpox foci found anywhere in Ethiopia. Except for the cases found in late July and early August in the nomad village at Dimo, none occurred in the Ogaden with an onset of illness after July; in the highlands the last case had occurred on 5 July. Search teams, posted in each *awraja*, were able to intensify their efforts in September and October as the seasonal rains ended, but still no cases were found.

Plans were made to hold a press conference at the end of October 1976 in the expectation that an announcement could be made that 10 weeks had elapsed since the onset of what was believed to be the world's last case of smallpox. Confirmation of eradication would require 2 full years of search, but week by week it appeared increasingly certain that no further cases would be discovered. Television crews flew to Dimo to take pictures of the village and of the last known patient, Amina Salat.

In late September plans were abruptly changed when cases of smallpox were reported from Mogadishu, the capital of Somalia. Initial disappointment that a few last imported cases had necessitated delay of the announcement turned to despair as it gradually became apparent that Somalia had endemic smallpox. Despite assurances to the contrary, neither surveillance nor vaccination activities had been well conducted. It had been anticipated that the last chapter of the global eradication of smallpox would be written in Ethiopia—but it was not to be.

Morbidity and Mortality Data

From the time the programme began, data collected from all households in which cases occurred included the name, age and sex of all residents and their past experience with regard to smallpox, vaccination and variolation. Data from Ethiopia are, in fact, more

Plate 21.13. National and international staff planning search strategy around last foci of smallpox in Ethiopia. *Left to right:* Zewde Besha, Muchie Kidanu, Mitiku Haile, C. do Amaral.

complete than those from any other country which experienced extensive endemic smallpox. Information on the age and outcome of illness are available for 54 991 of the 58 031 cases reported from 1971 to 1976 (Table 21.12). One-fourth of all cases (26%) occurred among persons aged 15 years and over who comprised 57% of the population. The large proportion of cases among adults is characteristic of an area in which the presence of smallpox was infrequent among much of the population. The proportion of cases among those less than 1 year of age (2%) is almost certainly understated because, in many areas, very young children with smallpox were often hidden from investigators.

Only variola minor was observed. No outbreaks were discovered with case-fatality rates comparable to those in Asia or western Africa. The overall case-fatality rate was calculated at 1.5%. The true figure may, however, be somewhat higher because outbreaks that occurred in the early years of the programme were not observed throughout their course and the deaths of some patients during the second or third week of illness may have been missed. Nevertheless, it is doubtful that the actual rate was much higher than 2%, a rate characteristic of variola minor.

Cases occurred almost exclusively among the "never vaccinated" group, only 961 of 49 106 persons of known vaccination status having previously been vaccinated. Even some of those listed as "vaccinated" had been vaccinated too late in the incubation period of the disease to be protected. Of the total number of cases, 7.3% occurred among persons who had been variolated.

Secondary attack rates among susceptible individuals within families were comparable to those measured elsewhere. Nearly 80% of children under 15 years of age who were exposed in households contracted the disease. Lower secondary attack rates among adults (43.6%) may reflect diminished levels of exposure, but they may, in part, be understated because of the failure of adults to recall past infection (Table 21.13).

Comparatively few children under 15 years of age were immune because of previous smallpox, which suggests that the disease had not been widely prevalent for a number of years. Among household contacts of cases as a whole, approximately equal numbers were immune as a result of variolation and vaccination. Three times as many had previously experienced smallpox.

Finally, data regarding the source of infection of outbreaks (if known) revealed that the

Table 21.12. Ethiopia: number of reported cases of and deaths from smallpox and case-fatality rates, by age, 1971–1976

Age group (years)	Cases		Number of deaths	Case fatality rate (%)
	Number	%		
<1	1 322	2	105	7.9
1–4	13 501	25	241	1.8
5–14	26 087	47	144	0.6
≥15	14 081	26	348	2.5
Total	54 991[a]	100	838	1.5

[a] Data unavailable for an additional 3040 cases occurring in this period.

Table 21.13. Ethiopia: secondary attack rates among susceptible household contacts, by age, 1971–1974

Age group (years)	Number of household contacts[a]	Previous smallpox	Variolation	Vaccination	Number of susceptible persons	Number of cases	Attack rate (%)
<1	1 875	6	44	50	1 775	1 081	60.9
1–4	15 816	100	424	564	14 728	11 675	79.3
5–14	31 863	720	721	1 826	28 596	23 007	80.5
≥15	49 324	13 634	3 243	3 276	29 171	12 728	43.6
Total	98 878	14 460	4 432	5 716	74 270	48 491	65.3

[a] In 20 398 households.

disease rarely spread over long distances. Of 6957 outbreaks analysed, a source of infection was ascertained for 4565. Of these, the source of 3956 (87%) was from contact in the same *woreda* and of another 362 (8%) in the same *awraja*. Only 1 in 20 originated in another *awraja*.

Exportation of Cases

Ethiopia, as had been feared, was a source of infection for neighbouring countries. The Sudan, which had been smallpox-free in 1967 (see Chapter 18), was reinfected by cases from Ethiopia in 1967–1968 and the disease subsequently became endemic there. One additional importation occurred in the Sudan in December 1972 but was quickly contained. Kenya experienced 2 imported cases in 1970–1971 with 44 secondary cases; 2 imported cases and 2 further cases in 1973; and 1 imported case with 5 further cases in 1976 (see Chapter 19, Fig. 19.4).

The French Territory of the Afars and the Issas and Somalia were the most subject to importations. The former, in December 1971, recorded an outbreak of 104 cases following an importation; in 1973, 10 separate importations occurred with 4 secondary cases; and in March 1974, 12 cases were reported following 1 or possibly 2 importations. Somalia, from 1962 to 1972, recorded only 2 cases of smallpox (1966); the origin of these was unknown. However, from December 1972 to the end of August 1976, when Ethiopia detected its last case, 42 cases were reported, of which 38 were said to have been importations, the last of these occurring in March 1976, 5 months before Ethiopia interrupted transmission. No further cases were reported from Somalia until October. Those cases were said to have originated in Ethiopia but in fact, as was later discovered, endemic smallpox had by then become re-established in Somalia and the official reports of field investigations, at least during the latter part of 1976, were unreliable.

CONCLUSIONS

Ethiopia proved to be as formidable a challenge to the Intensified Smallpox Eradication Programme as any country in the world, and at every stage. For nearly 3 years, the government not only declined to discuss a possible eradication programme, but actively opposed it. The idea of a national programme was eventually accepted, with reluctance, and, when it was launched in 1971—the fifth year of the Intensified Programme—little support was given by the government either in resources or in commitment. For more than 3 years, a staff proportionately smaller in number than in any other endemic country struggled valiantly, but with remarkable success, to contain the disease in one of the most rugged and difficult terrains in the world and among hostile populations to whom vaccination was all but unknown. Escalating civil war and famine further confounded the endeavour. The fact that the disease was of the mild variola minor variety increased the difficulty, because the population was not particularly eager to be vaccinated; many who were ill with smallpox were able to travel widely, spreading the disease as they went. Adequate resources could not be made available until late in 1975, but with much of the country then smallpox-free, less than a year elapsed before transmission was interrupted. Subsequently, search activities to certify the absence of smallpox were well supported by the government and resources for the task became available. But less than a year later, in 1977, the Somali-Ethiopian war broke out, rendering inaccessible a large portion of the area in which the last cases had occurred. Only through a surveillance programme conducted from bases in Somalia was it possible to continue activities in the troubled Ogaden desert and to confirm the absence of smallpox.

It is a tribute to a dedicated WHO staff and a small band of extraordinarily capable Ethiopian health officers and sanitarians that programme activities were continued at all during several years in many parts of the country. For many years and in many areas, smallpox eradication was virtually the only health programme in operation in the field, and WHO smallpox staff were almost the only expatriate workers who ventured outside the major cities.

Global smallpox eradication was in jeopardy on numerous occasions and in many countries, but nowhere was the outcome so greatly in doubt, and for so long, as in Ethiopia.

Prospects for the successful interruption of smallpox transmission in Yemen had not originally appeared to be much more encour-

aging than in Ethiopia, and indeed the programme, such as it was, was reasonably well executed only during its first year. Yemen, however, was far smaller in size and population; variola major, rather than variola minor, had predominated but apparently had spontaneously died out before the programme began. In Democratic Yemen, whose population was even smaller than that of Yemen, the WHO-supported programme was better executed, but its achievement primarily consisted in confirming the absence of smallpox.

In retrospect, it would have paid rich dividends strategically if, in Ethiopia, greater attention had been paid to smallpox in the Ogaden desert area at an earlier stage. The most competent staff and the larger proportion of resources were initially assigned to the difficult mountainous plateau areas of the north in the expectation that smallpox transmission would soon terminate—for the most part spontaneously—among the desert nomads. Until March 1976 the programme in the Ogaden was modest and, as became evident, not well organized. When a fully effective programme did take shape, it was soon discovered that vaccinial immunity was far lower than had been recorded, reporting was poor and containment ineffective. Smallpox continued to spread among nomads, but in August 1976 the last known outbreak was finally contained. This would have marked the end of smallpox if the WHO-supported programme in Somalia had been conducted as well as it was reported to have been. However, uncontained importations into Somalia set the stage for yet one more major programme in a country that had previously been free of smallpox. These events are the subject of the next chapter.

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CHAPTER 22

SOMALIA AND DJIBOUTI

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INTRODUCTION

Unexpectedly, the final episode in the global eradication of smallpox did not take place in one of the countries which had recently been so heavily infected, but in Somalia, whose first endemic cases in 14 years were reported in late September 1976. The reports were received 7 weeks after the last outbreak in Ethiopia, at a time when WHO was preparing to announce that, subject to confirmatory search, the world was free of smallpox. It was a bitterly disappointing setback, coming as it did at the end of a 12-month period that had witnessed the occurrence of the last case of variola major in Asia and the conclusion of a difficult but successful campaign in Ethiopia, then thought to be the world's only remaining endemic country. For Somalia to be identified as the last country with endemic smallpox was an embarrassment to its government. It was especially distressing to Somalia's health services, which for years had been sharply, and sometimes justifiably, critical of the programme conducted in adjacent areas of the Ogaden desert by the Ethiopians.

Since 1969 Somalia had been engaged in a WHO-assisted programme of smallpox vaccination and surveillance which national programme staff believed to be highly successful. As late as August 1975, the national programme director, in a meeting with Ethiopian staff at the border of the two countries, reported that 85% of the population had been successfully vaccinated. Although importations of smallpox had been frequent, most of the cases were said to have been detected within a few days of onset. They had occurred among nomads, who roamed freely across the vast Ogaden desert. Between 1972 and February 1976, 38 imported cases were acknowledged but only 4 secondary cases were said to have occurred. No cases were reported between February and September 1976, although later evidence suggests that it was during these months that endemic smallpox became re-established. In September, Somalia's report of smallpox cases brought the prompt assistance of experienced WHO epi-

demiologists. These staff members were handicapped by not being permitted to visit the sites of outbreaks or to travel widely in search of cases, but with their Somali counterparts they struggled to interrupt what seemed to be a few tenuous chains of transmission in Mogadishu, the capital. By January 1977, it appeared that they had succeeded. However, a country-wide search for cases was called for, and in March the government agreed to cooperate fully in making this possible. The search soon revealed that endemic smallpox extended throughout southern Somalia. Major epidemics followed, and in May the government declared an emergency.

An intensive operation was therefore started which brought support from many countries and agencies and assistance from WHO epidemiologists who had worked in other endemic countries. The government gave its full support, and on 26 October 1977, only 141 days after the emergency had been declared, the world's last case of endemic smallpox occurred. Meanwhile, more than 3000 cases had been recorded.

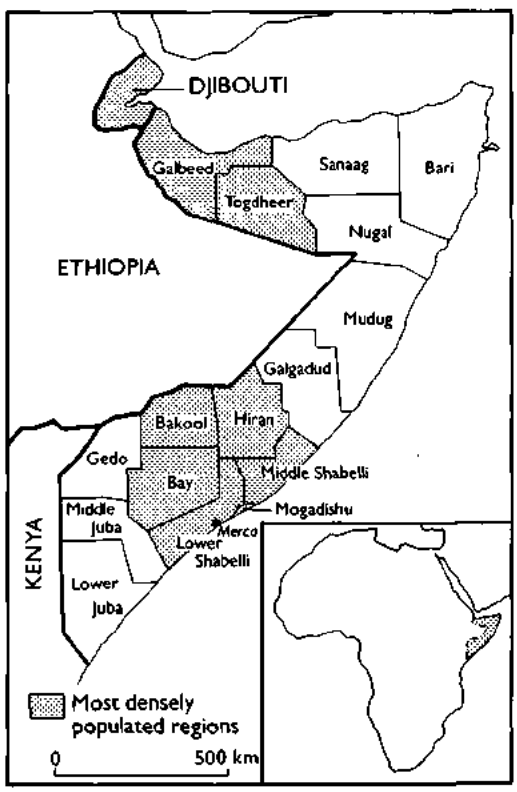

Fig. 22.1. Somalia: Regions and adjacent countries. Before attaining independence in 1977, Djibouti had been the French Territory of the Afars and the Issas.

This chapter deals with events in Somalia and, briefly, with the situation in the adjacent French Territory of the Afars and the Issas, which became the independent state of Djibouti in 1977 (Fig. 22.1). The latter country, with a population (1977) of 240 000, experienced periodic importations of smallpox from Ethiopia but the disease never became endemic. Outbreaks were controlled by containment vaccination; mass campaigns were conducted every 3 years.

For a detailed account of the Somalia programme, the reader is referred to the book *Smallpox Eradication in Somalia* (Ježek et al., 1981), from which much of the information in this chapter is derived.

BACKGROUND

The Somali people, who were predominantly nomadic and semi-nomadic pastoralists, roamed across the largely open and unmarked borders of the Horn of Africa in areas that included Somalia, parts of Djibouti, Ethiopia and Kenya. In 1960, when the country became independent, Somalia comprised the former British Somaliland Protectorate and the United Nations Trust Territory of Somalia, once an Italian colony. Thus, English was widely understood in the north and Italian in the south. Following a military coup in 1969, the country was administered by a Supreme Revolutionary Council and renamed the Somali Democratic Republic. The Somali Revolutionary Socialist Party was founded in July 1976 and provided political and administrative leadership throughout the country's 16 regions and 83 districts. The government's idea of uniting all the Somali peoples in one nation, regardless of existing political boundaries, was a source of contention with neighbouring countries throughout the course of the Intensified Smallpox Eradication Programme. This controversy was manifested in the continuing tension between Somalia and Ethiopia and in guerrilla warfare in areas of Ethiopia adjacent to Somalia in which Somali nomads lived.

Population Movements and Health Facilities

Nomadic pastoralists, who constituted about half Somalia's population (3.1 million

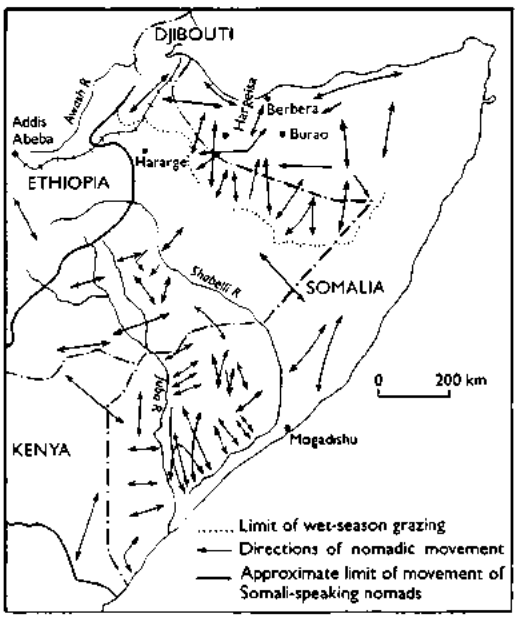

Fig. 22.2. Horn of Africa: approximate area covered by movements of Somali-speaking nomadic pastoralists.

persons in 1975), played an important role in sustaining smallpox transmission, carrying it from one area to another, where it spread among settled populations. An indication of the extent of pastoralism is provided by estimates (1975) of the numbers of livestock -3.5 million camels, 15 million goats and sheep, and 4.5 million head of cattle. A large proportion of the settled population was located along the coast in some 60 towns and cities, which were designated as municipal centres. Fewer than 25 of these, however, had more than 5000 inhabitants; by far the largest was Mogadishu (population, 450 000). Small settlements were also found along roads and in an agricultural area in southern Somalia. It was the south that was afflicted by the 1977 epidemic.

The population of Somalia was most heavily concentrated between the Juba and Shabelli rivers in the south and in areas to the south-east of the French Territory of the Afars and the Issas in the north. About 1.5 million people lived in the most heavily populated areas in the south and about 900 000 in the north. The rest were widely scattered over a vast, arid scrub desert in which population densities seldom exceeded 1 or 2 persons per square kilometre. Travel between the northern and southern areas was infrequent. During the dry season, the nomadic population in the north congregated near deep wells, primarily within Somalia; during the March June rainy season, they travelled south and settled widely over a grassy well-watered plateau area in Ethiopia (Fig. 22.2). In the south, the pattern of movement was more complex. Nomads

Plate 22.1. The unpredictable movements of Somali nomads made the search for cases difficult. Their huts were easily carried on camel-back (**A**) and quickly erected (**B**).

located west of the Juba river travelled to more westerly districts and into Kenya in the rainy season. During this period, those living between the two rivers dispersed widely throughout the area because of the hordes of insects, especially the riverine species of tsetse flies, which infested the river banks and localities with standing water. The nomads whose herds consisted only of camels or cattle moved more or less constantly throughout the year. Others, termed "semi-nomads," had mixed herds of camels, cattle, sheep and goats and settled during the crop-growing season to cultivate arable land.

The movements of nomads, particularly in the south, were unpredictable, even from one day to the next. This made it exceptionally difficult to conduct any sort of systematic programme, either of case detection or of vaccination, especially during the rainy season, when roads became all but impassable. The rains fell irregularly, sometimes consisting of scattered localized downpours extending over only a few square kilometres. The different nomadic groups competed for the scarce vegetation and each had several searchers who roamed extensively. When rains fell in an area, the report of a searcher might cause an entire group to dismantle its camp, pack up its belongings and move 50 kilometres or more over a period lasting several days. Moreover, the nomadic groups, often consisting of only 3 or 4 families, frequently broke up into smaller subgroups for the sake of mobility, and families often shifted from one group to another. Although the women, girls and small children stayed in the camps, the men and older boys accompanied the herds; the younger men, who herded the camels, frequently ranged over great distances.

During the time of the smallpox eradication programme in Somalia, there were 4 other factors which led to substantial movements of population. The first was the seasonal need in the south for large numbers of agricultural labourers, which brought nomads and others from sparsely settled areas to the banana and sugar-cane plantations. The second was severe drought, which occurred throughout the Ogaden desert in 1974–1975 and led to the migration from the Ethiopian portion of the Ogaden of an estimated 200 000–300 000 persons, many of whom were accommodated and fed in refugee camps (Plate 22.2) in Somalia and the French Territory of the Afars and the Issas. The third was the Somali–Ethiopian war, which began

UNHCR / W. GAPTUNG

Plate 22.2. Laas Dhurre camp, Hargeisa District, Somalia. War and famine drove thousands of refugees out of Ethiopia.

in 1977 and resulted in tens of thousands of refugees fleeing into border areas of Somalia and Djibouti. The fourth was a programme, launched in 1975, to resettle upwards of 100 000 nomads in southern agricultural areas.

Health services in the two countries were much more extensive than in Ethiopia. In Somalia in 1968, there were 21 hospitals and 187 health posts and dispensaries with more than 1300 trained health personnel. In the French Territory of the Afars and the Issas, there were 6 hospitals and 16 dispensaries and a health staff of 450 persons, including 41 physicians. The Somali road network—also more extensive than in Ethiopia—consisted of 2000 kilometres of asphalt-surfaced roads and 4000 kilometres of gravel and earth roads.

Smallpox and its Control before 1969

As was the case in most countries, reporting systems in Somalia and the French Territory of the Afars and the Issas were poor and data on smallpox are incomplete. Variola minor was said to have been the predominant form during recent decades and, in some areas, health staff differentiated between the more severe cases, which they called "true smallpox", and the less severe, which they called "alastrim". Because cases of variola minor were often not reported as smallpox, this distinction undoubtedly contributed to underreporting. From the available data, it appears that endemic transmission in Somalia ceased in about 1962 (Table 22.1). The French Territory of the Afars and the Issas—at least since 1930—experienced only rare sporadic outbreaks following importations, but 2 outbreaks, in 1959 and 1966, are of special interest. Both resulted from importations from Ethiopia and occurred over a 2-month period. The first consisted of 110 cases with 13 deaths (11.8%), and the second of 52 cases with 6 deaths (11.5%). The two outbreaks and the report of a single outbreak in Ethiopia in 1964 (Teclemariam, 1965) provide the only documentary evidence of the persistence of variola major in Ethiopia or the Horn of Africa after about 1955. Apart from the 1966 outbreak in the French Territory of the Afars and the Issas, during which the disease was imported into Somalia, no cases of smallpox were recorded in either country between 1963 and 1971.

Table 22.1. Somalia and the French Territory of the Afars and the Issas: numbers of reported cases of and deaths from smallpox, 1962–1978

Year	Somalia		French Territory of the Afars and the Issas (Djibouti)	
	Number of cases	Number of deaths	Number of cases	Number of deaths
1962	221	..[a]	0	0
1963	0	0	0	0
1964	0	0	0	0
1965	0	0	0	0
1966	2	0	52	6
1967	0	0	0	0
1968	0	0	0	0
1969	0	0	0	0
1970	0	0	0	0
1971	0	0	26	3
1972	5	0	79	0
1973	7	0	14	0
1974	11	0	12	0
1975	14	0	0	0
1976	39	1	0	0
1977	3 229	13	0	0
1978	0	0	0	0
Total	3 528	14	183	9

[a] .. = data not available.

The infrequent occurrence of smallpox in the French Territory of the Afars and the Issas and the cessation of transmission in Somalia in 1962 could not be attributed to national vaccination campaigns. Both countries offered vaccination for those travelling abroad and conducted localized vaccination campaigns when outbreaks occurred. The French Territory of the Afars and the Issas carried out its first country-wide campaign in 1966, during which 115 000 people were vaccinated; thereafter, campaigns using freeze-dried vaccine were conducted every 3 years, each resulting in the vaccination of 100 000–120 000 persons. Somalia, using a locally produced liquid vaccine until 1966, vaccinated only 20 000–50 000 persons a year, primarily the inhabitants of major towns who required vaccination certificates for travel. In addition, because of outbreaks, special vaccination campaigns were conducted in 1962 near the Kenyan frontier and in 1966 near the border of the French Territory of the Afars and the Issas and in Mogadishu. During the latter campaign, 194 000 persons were vaccinated, but with vaccine of dubious quality; a study carried out in 1967 revealed that only 14% of those given primary vaccination had had successful takes.

Special vaccination scar surveys (Table 22.2) conducted in 1967 by a WHO medical

Table 22.2. Somalia: results of vaccination scar surveys, by age group, 1967 and 1968

Age group (years)	% of population with vaccination scars, 1967		Age group (years)	% of population with vaccination scars, 1968
	Rural	Urban		Rural
0–7	0	49	0–4	2
8–14	46	52	5–14	37
⩾15	58	45	⩾15	48

officer and in 1968 by United States Peace Corps volunteers showed that vaccinial immunity was poor even among the rural settled population of Somalia. It was undoubtedly much lower among the nomads.

Until the early 1960s variolation had been widely practised when outbreaks of smallpox occurred. However, no evidence of active variolation was discovered in either country during the 1970s, although as recently as August 1976, Ethiopian staff observed the practice in a Somali-speaking nomad group in the Ogaden desert in Ethiopia (see Chapter 21).

Despite the low level of vaccinial immunity and the proximity of these countries to Ethiopia, which was heavily endemic, the continuing transmission of smallpox had apparently ceased. Imported cases were few, although, because notification systems were poor, it is likely that more occurred than were reported. Long-sustained endemic spread did not, however, develop, the only reasonable explanation for this being that the susceptible population was too widely dispersed for transmission to be sustained. The long absence of endemic smallpox bred an unwarranted confidence among national and WHO staff alike that the disease would not re-establish itself even if it were imported. Similarly, Ethiopian staff were comparatively unconcerned about smallpox among Somali-speaking nomads in Ethiopia and until 1976 gave little priority to their programme in the Ogaden desert.

THE COMMENCEMENT OF THE SMALLPOX ERADICATION PROGRAMME, 1969

Because of the smallpox situation in the neighbouring country of Ethiopia, the development of an eradication programme in Somalia was considered important. The government expressed interest, and a WHO consultant visited the country in January 1968 to formulate a plan of operations. This called for a 3-year national vaccination campaign, from 1969 to 1971, coupled with routine assessment of vaccination coverage, as well as the development of a reporting system and surveillance activities. WHO agreed to provide an adviser, vehicles, equipment and vaccine; to meet the necessary operating costs; and to pay a supplementary per diem allowance for all Somali staff when they travelled in the field. Up to the end of 1976, WHO's annual contribution to the programme was modest (Table 22.3) but adequate, in view of the country's small population.

The plan of operations was similar to many other such plans in the Intensified Programme. It called for vaccination to be performed by mobile teams moving in groups from village to village and from house to house. This would serve to protect the settled population, although little thought was given in the plan to the vaccination of nomads, who comprised half the total population. It was decided simply to vaccinate those who were found at water-holes or encountered by chance when the teams were on their travels. From later observation, it was apparent that only a small proportion of the nomads could have been vaccinated by this approach, a deficiency in the campaign which might have been discovered and corrected if the assessment of coverage had been well conducted. The problem was not pursued until 1977.

The vaccination campaign was slow in starting and never functioned well (Table

Table 22.3. Somalia: expenditure by WHO for smallpox eradication and number of doses of vaccine supplied, 1967–1979

Year	Expenditure (US$)	Number of doses of vaccine
1967–1968	51 184	96 000
1969	25 127	35 000
1970	16 565	370 000
1971	17 445	105 000
1972	32 980	622 000
1973	26 141	624 000
1974	28 306	650 000
1975	51 781	608 000
1976	98 853	1 151 000
1977	2 193 648	3 904 000
1978	1 788 242	1 524 000
1979	2 140 157	—
Total	6 470 429	9 689 000

Table 22.4. Somalia: number of vaccinations performed, 1969–1978

Year	Number of vaccinations
1969	79 974
1970	645 862
1971	475 988
1972	712 045
1973	850 000[a]
1974	704 207
1975	660 000[a]
1976	320 000[a]
1977	994 713
1978	566 203

[a] Includes estimates for one or more months during the year.

22.4). A WHO smallpox adviser arrived in June 1968 to assist with operations, but the campaign was not launched until August 1969. It began in Mogadishu, where 6 teams with 33 workers took nearly 6 months to vaccinate the city's population. Thereafter, 20 vaccinators began work along the Kenyan border, and in May 1970 a group of 12 workers started to vaccinate people in the north of the country. However, the campaign was suspended in November 1970, when cholera began to occur and the teams were directed to administer cholera vaccine. In June 1971 the smallpox vaccination campaign was resumed and by the beginning of 1974, the teams had completed 2 tours of the country. By the end of that year nearly 3.5 million smallpox vaccinations had been recorded, a number which was approximately equivalent to the population.

The number of vaccinations in relation to population would suggest that a reasonably high degree of vaccinial immunity must have been attained by the end of 1974. However, attempts to confirm this by assessment were never diligently pursued. From information that became available in 1977, it would appear that the coverage in settled populations was at best 60–80%; among nomads in the south, it ranged from 10% to 20%.

During 1974 the smallpox vaccination teams were disbanded and their members dispersed throughout the country initially to participate in a national literacy campaign, and then, after a severe drought in 1974–1975, to help in refugee and relief camps. Finally, at the end of 1975 some of the staff returned to full-time duties with the smallpox eradication programme. At that time, 2 teams of 4 persons began a campaign of both smallpox and BCG vaccination, one team working near border areas in the north and the other in the south. While vaccinating, they searched for cases. With so few personnel engaged, less than one-third of the country could be visited in the course of a year.

No cases were reported in either the French Territory of the Afars and the Issas or Somalia from 1967 until late 1971. However, between November 1971 and July 1976, the two countries together reported 173 cases, the former reporting 131 cases, of which 16 were believed to have been importations from Ethiopia, and Somalia 42 cases, of which 38 were said also to have been imported from Ethiopia. It is probable that there were other cases, since neither country had an organized notification system or an active programme of case detection. Reporting was further compromised because the cases were of the mild variola minor type and some nomadic groups concealed infected persons to avoid being ostracized by other groups, as was the custom when variola major was present.

The first case to be reported for more than 4 years in either country was detected in mid-November 1971 in Djibouti City in a recent arrival from the north of the Territory (Fig. 22.3). Later investigation suggested that smallpox had been introduced from Welo Province, Ethiopia. Other cases soon followed and by the time the outbreak had ended, on 29 February 1972, 104 cases had been documented. Most of them (79) were found in the city itself; the remainder occurred in 4 smaller rural outbreaks. A triennial mass vaccination campaign, scheduled to commence in January 1972, actually began some weeks earlier, and in a matter of a few months, 117 000 vaccinations had been performed.

In October 1972, another imported case from Ethiopia was detected in the French Territory of the Afars and the Issas, but this time secondary spread did not occur. Also in October—for the first time in 6 years—Somalia reported cases; the 5 patients concerned were said to have been infected in Hararge Province in Ethiopia. No secondary cases were reported.

During 1973, cases were imported into both countries. The French Territory of the Afars and the Issas reported 14 cases: 10 represented importations and 4 were among contacts, 3 of whom were infected while hospitalized. Somalia reported 7 cases, of which 6 occurred in the southern part of the country. Their place of origin in Ethiopia was unknown. As in 1972, all were said to have

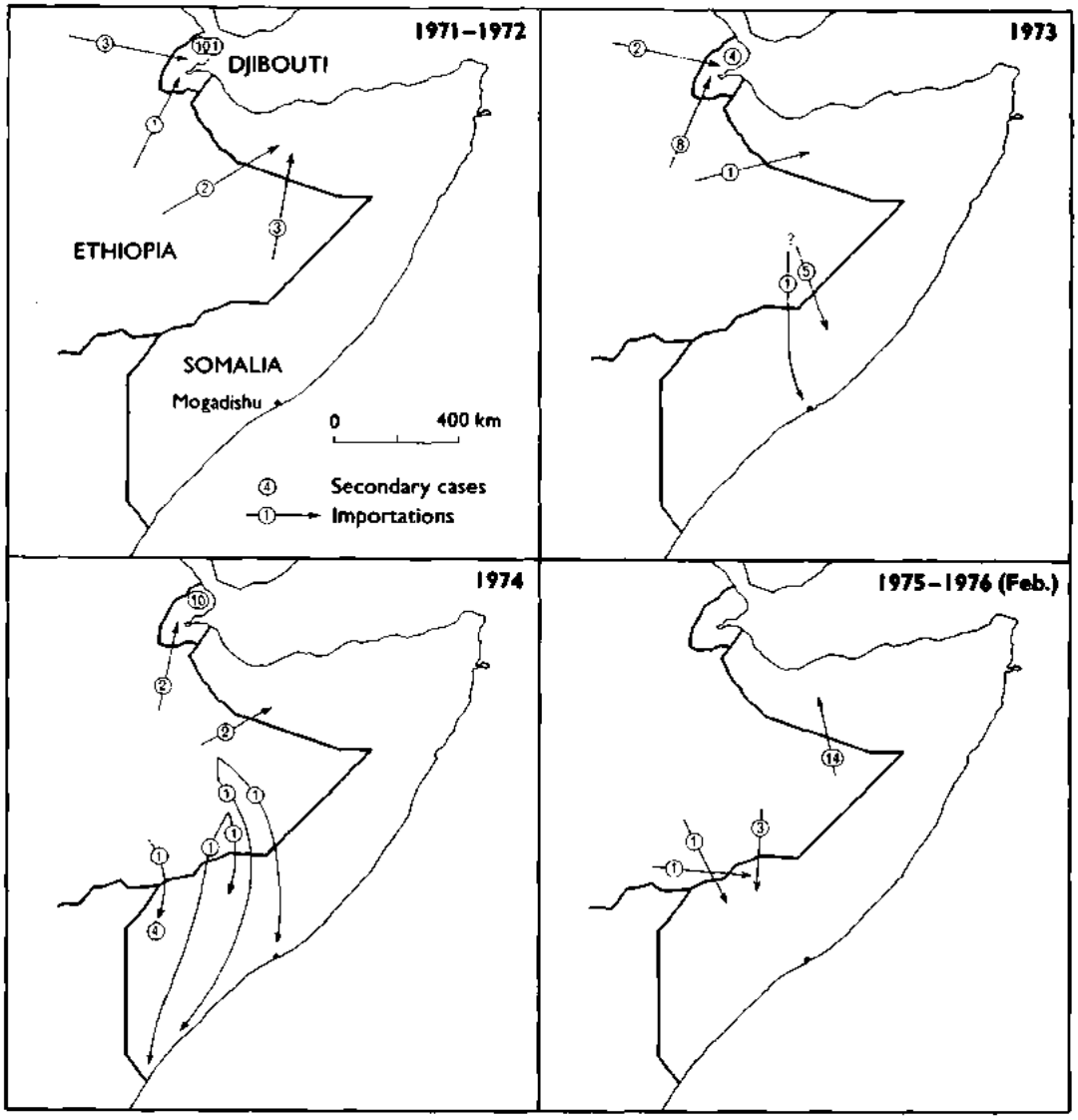

Fig. 22.3. Somalia and Djibouti: reported importations of smallpox, November 1971–February 1976.

been detected within a few days after the onset of rash and no secondary cases were reported.

In 1974 the French Territory of the Afars and the Issas reported another 12 cases, of which 2 were importations, the remainder resulting from the subsequent spread of infection. These were the last known cases in the Territory. Nine of the 11 cases in Somalia that year occurred in the southern part of the country, in parallel with a spread of smallpox in Ethiopia from the northern mountainous plateau into the southern Ogaden desert. For the first and only time Somalia reported 4 secondary cases, all close contacts in a single household.

From January 1975 to the end of February 1976, Somalia reported an additional 19 imported cases, many of which were in refugees in drought-relief camps, but no secondary cases were said to have occurred.

In 1975–1976, the Smallpox Eradication unit at WHO Headquarters became increasingly sceptical that the reports submitted to WHO from Somalia were complete or fully accurate. It seemed unbelievable that, between October 1972 and February 1976, Somalia could so quickly detect and contain

38 importations, with secondary spread occurring on only one occasion, given the paucity of staff and the lack of an organized surveillance programme. No other country had been so successful in the rapid detection and containment of imported cases. Moreover, data submitted to WHO regarding the dates of onset and dates of detection for 30 of the cases indicated that 20 were supposed to have been detected within 3 days after the onset of rash; yet even the most experienced clinicians had difficulty in identifying cases of smallpox so early in the course of the disease. Even in countries with an adequate surveillance system, cases were rarely detected and diagnosed until a week or more after onset. The reports from Somalia seemed too good to be true. The fact that some of the cases were first reported to WHO in Geneva through one of the embassies in Mogadishu but were not notified officially to the Organization until questions had been raised with the Somali government did nothing to increase confidence in the official reports.

Meanwhile, in letters from Henderson to the WHO regional smallpox adviser, copies of which were sent to the WHO smallpox adviser in Somalia, repeated attempts were made to obtain additional information about the status of the programme and the occurrence of cases, and advice was offered as to the methods that should be adopted in the investigation, containment and notification of outbreaks. One letter, dated 23 February 1976, is of special interest in view of subsequent events:

"The occurrence of 4 importations into Somalia during the course of only a few weeks is both surprising and alarming. It suggests indeed that many more may occur and unless due care is taken, I believe there is a very real risk that Somalia might become epidemic... I am very concerned that Somalia should not become an endemic area just at that point when we believe the problem in Ethiopia is coming under control. The memory of Botswana becoming reinfected just at that point when the last cases in South Africa were occurring is too fresh!"

Somalia reported a case in February 1976 but no others were notified during the next 6 months. No reports were received from embassy sources, which had, in the past, been reasonably prompt and accurate in forwarding information. In retrospect, greater efforts should have been made during this period to assess the problem through personal visits but because of the complex logistics of the final phase of the Intensified Programme in Ethiopia and a range of activities concerned with the certification of eradication in many different countries, the attention of WHO Headquarters and regional smallpox eradication staff was diverted from a country which was apparently free of the disease.

At some point in 1976 smallpox became reestablished in Somalia. It could not be determined exactly when this occurred, and information about the cases could not be obtained. Political problems played a role in inhibiting surveillance and the reporting of cases. In the Ethiopian portion of the Ogaden desert, the Western Somalia Liberation Front had been formed in the early 1970s and a liaison office set up in Mogadishu. Training camps were established in Somalia near the border with Ethiopia, and guerrilla forces as well as nomads began moving back and forth across the border in larger numbers. In 1976–1977, guerrilla warfare steadily intensified, eventually culminating in the occupation of the Ethiopian portion of the Ogaden desert by the Somali army in July 1977.

THE SMALLPOX OUTBREAK IN MOGADISHU, SEPTEMBER 1976

After the last known case of smallpox occurred in Ethiopia, on 9 August 1976, 7 weeks passed during which no case was reported from anywhere in the world. Specimens from patients with rash and fever in many countries were received daily by the WHO Smallpox Eradication unit in Geneva and dispatched to the reference laboratories in Atlanta and Moscow. None of them showed evidence of poxvirus until 27 September, when the Atlanta reference laboratory reported the presence of poxvirus in 2 specimens from Somalia. Henderson immediately sent the following cable to Mogadishu:

"POXVIRUS PARTICLES PRESENT BOTH SPECIMENS STOP DIAGNOSIS OF SMALLPOX VIRTUALLY CERTAIN STOP URGENT THAT EVERY CONTACT SINCE RASH ONSET BE FOUND AND VACCINATED INCLUDING ALL HOSPITAL PATIENTS STOP SITUATION MOST CRITICAL SINCE NO SMALLPOX SINCE 9 AUGUST IN ETHIOPIA STOP ESSENTIAL DETERMINE WHERE BOTH PATIENTS WERE EACH DAY FROM SEVEN TO SEVENTEEN DAYS BEFORE ONSET STOP SUSPECT BOTH EXPOSED SAME LOCATION

STOP HIDDEN FOCUS MUST BE PRESENT NEAR BORDER OR POSSIBLY ELSEWHERE STOP THIS COULD BE WORLDS LAST FOCUS STOP ESSENTIAL THIS BE FOUND AND CONTAINED URGENTLY STOP ARITA DEPARTING EARLIEST POSSIBLE FLIGHT TO ASSIST."

Arita departed for Somalia forthwith to help in the investigation, and telephone and telex messages between Geneva and Mogadishu began to be exchanged daily.

By the end of September, 5 patients who had experienced the onset of smallpox between 30 August and 23 September had been placed in an isolation hospital in Mogadishu. The first 2 entered hospital on 1 and 14 September respectively; these were the patients from whom the first specimens had been taken. The remaining 3 were hospitalized between 20 and 25 September.

The 5 patients, ranging in age from 16 to 70 years, were questioned repeatedly by Arita and Somali staff in an effort to determine where they might have contracted the infection. They all claimed to have been living in one or the other of two areas in Ethiopia and said that 8–10 days before the onset of illness they had travelled to the Somali border on foot and thence had taken a bus to Mogadishu, a distance of 400 kilometres (Fig. 22.4). Two patients were said to have reported seeing other people with a similar type of rash in areas of Ethiopia from which they said they had come. The two areas thus identified were situated in the desert, one lying south-west of Dimo, the site of the last known outbreak in Ethiopia, and the other further to the south-east, near the border. The reports were plausible. Ethiopian teams had been actively searching for many months throughout most of the Ogaden except in the province in which the two suspect areas were located. There, search operations had been delayed until August 1976 by guerrilla warfare and were somewhat hampered thereafter.

Arita immediately travelled to the Somali–Ethiopian border to contact WHO epidemiologists working in the Ethiopian part of the Ogaden desert. By conveying to them in detail the information obtained from the 5 patients, he hoped that the focus in Ethiopia might be quickly located and contained. An extensive search in Ethiopia was promptly undertaken by a staff which included 8 Ethiopian sanitarians, 5 WHO epidemiologists and 150 search workers using vehicles, helicopters and a fixed-wing aircraft. The entire area was searched repeatedly over a 6-month period, but no evidence that smallpox had been present after July 1976 could be found.

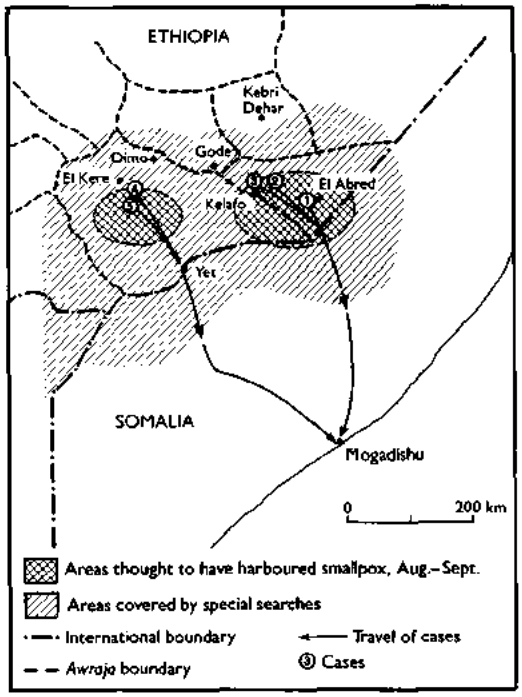

Fig. 22.4. Ethiopia and Somalia: areas thought to have harboured smallpox and areas searched, 1976.

A more accurate, although still incomplete, account of what had actually happened did not become available for many months, indeed years. The search for a source of infection in Ethiopia had, in fact, been futile because, by then, endemic smallpox had already become established in Somalia, a fact known both to Somali staff and to the WHO smallpox adviser.

For Somalia at that time to admit to the existence of cases was awkward for both the political leaders and the national health staff. With tension mounting between Somalia and Ethiopia, the periodic meetings of national smallpox eradication staff from the two countries at border posts had become increasingly acrimonious, as each expressed doubts about the quality of the other's programme. In September, Somali programme staff simply did not believe that Ethiopia had become smallpox-free. A letter dated 11 November 1976 from the WHO representative in Somalia to the Director of the WHO Re-

gional Office for the Eastern Mediterranean, reflected the prevailing emotional climate:

"Government authorities have resented the fact that Ethiopia has been declared free from smallpox, almost at the same time as Somalia was declared as the last known infected focus in the world. This is viewed as some kind of international conspiracy and the influx of WHO smallpox experts as adverse publicity for Somalia."

Reports later received by WHO field staff indicated that other suspected cases of smallpox had been hospitalized as early as June 1976, and less definite information suggested that there had been other unreported cases, indeed sizeable outbreaks, earlier in the year. Somali staff had hoped that containment could be achieved without publicizing the outbreaks, thus avoiding the stigma of Somalia's being identified as the last infected country. As in other countries that sought to contain outbreaks while suppressing information about their existence, the outcome was disastrous.

With smallpox known to have been prevalent in Somalia for many months, it is curious that a decision was made, on 14 September 1976, to obtain specimens from 2 patients and to submit them to WHO for laboratory examination. Three events appear to have been responsible: first, the receipt of a letter from Henderson informing Somali programme staff about a projected news conference to announce that the world's last case of smallpox might now have occurred; secondly, the arrival in Mogadishu of Dr Bert van Ramshorst, a WHO smallpox adviser with the Ethiopian programme who had been seized by the Somali border police; and thirdly, the first occurrence of smallpox cases in the capital city. Henderson's letter, dated 30 August, was addressed to the regional smallpox adviser at the WHO Regional Office for the Eastern Mediterranean in Alexandria, and a copy was sent to Mogadishu:

"As the days go by, it seems increasingly possible that the Bale [Ethiopia] case with onset on 9 August 1976 could be the world's last case of smallpox ... my guess would be that it will be difficult to have reasonable confidence about this until late October. When we do reach [that] point, the Director-General would like to make a major announcement with maximum possible news coverage... Such an announcement conceivably could be made jointly with the Secretary-General at the [United Nations] General Assembly ... one would not wish to make an announcement that there are no known smallpox foci without having reasonable confidence that another outbreak would not emerge one or two weeks later. We know, of course, that we cannot have full confidence until at least two years have elapsed... [but] the provisional announcement, which would be highly newsworthy, could come, I believe, as early as late October."

That the programme in Ethiopia might be better than Somali officials had believed was confirmed by Dr van Ramshorst. The report of the WHO smallpox adviser in Somalia, dated 16 September 1976, to the regional director is of interest:

"Dr van Ramshorst crossed into the Somali territory on the afternoon of 8 September 1976 near Abu Duaaq. He was detained by border police and handed over to security authorities who brought him to Mogadishu the same night. He was in Mogadishu from 9 to 13 September before RR UNDP [Resident Representative, United Nations Development Programme] was informed about his detention ... During Dr van Ramshorst's stay in Mogadishu, we have made some useful exchange of information ... I was able to arrange a meeting with the Minister. The Minister was favourably impressed with the zeal and enthusiasm demonstrated by Dr van Ramshorst in the pursuance of the objectives of the programme ... for the first time the Somali health authorities have now appreciated the effort that is being put into the programme on the other side of the border."

The possibility that Ethiopia might be free of smallpox could no longer be discounted. The discovery of smallpox cases in Somalia after an announcement by the Director-General of WHO that smallpox appeared to have been eradicated would have been most embarrassing. The concealment of the outbreak in Somalia could continue no longer.

Initial Containment Measures

Somali programme teams assisted by 2 WHO advisers endeavoured to find the source of infection of the 5 cases and, still believing that it was in Ethiopia or along the Somali side of the border, undertook a 3-day search in border areas in Somalia, from 3 to 6 October 1976, but discovered no cases. They reported that 80–90% of the villagers whom they saw had vaccination scars. A more intensive search was deemed necessary, and 32 staff and a WHO epidemiologist, provided with 4 vehicles, were assigned to the task. The

Plate 22.3. The WHO smallpox recognition card was abundantly used by the Somali search teams inquiring about possible cases of smallpox.

search began on 9 October and was completed on 2 November. It ranged over an area about 500 kilometres long by 100 kilometres wide but revealed no cases. In all, some 12 000 persons were seen in approximately 30 different villages; 74% had vaccination scars. Of 1200 nomads seen at watering-places, 68% had previously been vaccinated. All denied having seen cases of smallpox for 2 years or more.

Meanwhile, house-to-house night-time searches were conducted in Mogadishu on 18 and 25 October (Fig. 22.5) utilizing 60 programme staff in the northern part of the city, in which the cases had been discovered, and 2000 other staff, including police, to search the other areas.

Cases continued to be admitted to hospital and by the end of October, 20 had been officially reported (Fig. 22.6). The sources of infection of only 10 cases could be documented. Careful investigation, search and vaccination in and immediately around the dwelling of each patient were urgently required. The WHO epidemiologists were skilled in this approach but were not permitted to accompany Somali health staff in visits to houses in the city or in questioning patients at the hospital. Containment was less than optimum because vaccination was conducted only during the daylight hours, when most adults were away from home. To help in detecting cases, WHO staff proposed that a reward should be offered to anyone reporting a case, but this proposal was not accepted.

The persistence of cases led to a city-wide vaccination campaign extending from 28 October to 15 November, and this was followed on 16 November by yet another night search. Only 9 cases of smallpox were reported in November, and for 8 of them the source of infection could be clearly identified. It was hoped that the outbreak might be coming to an end but, as it was later learned, the notification of cases continued to be suppressed. Smallpox patients were then being admitted to two different parts of the hospital, one in which cases were officially reported and another in which they were not. Officially 34 cases were registered as having been hospitalized in 1976; the unofficial hospital register, not made available until 1978, showed the actual number to have been more than 500.

The continuing failure to discover the source of infection of what was thought to

have been the first 5 importations into Mogadishu was most disturbing at the time. It was claimed that the foci had been in Ethiopia but no evidence of smallpox had been found there since early August. The most reasonable explanation, seemingly, was that the cases had occurred among nomadic groups which had moved elsewhere before the search. With the passage of time, it was thought that such groups might well have penetrated far into Somalia. Search of the border regions in Somalia had failed to detect cases and none had been reported subsequently by 5 Somali mobile teams then working outside Mogadishu. However, no systematic search had yet been conducted in the 5 other administrative regions of southern Somalia. Accordingly, WHO proposed to the health authorities that such a search should be undertaken, with support from 2 additional experienced WHO epidemiologists who had recently arrived in Mogadishu. A plan was elaborated by Somali and WHO staff which called on WHO to provide 10 more vehicles, to be obtained through emergency local purchase in Kenya, and to cover the necessary local costs. An expenditure of US$350 000 was envisaged. On 11 November the Director-General of WHO, in a telegram to the Minister of Health, approved the expenditure, ending on the encouraging note that it was to be hoped that the concerted effort over the next 2 months would be sufficiently intensive to identify clearly and to interrupt the links in the chain of transmission. If this proved successful and it could be asserted with confidence that no hidden foci existed, he would plan to make a formal announcement at the January 1977 meeting of the WHO Executive Board that the world's last smallpox foci had been eliminated. The Minister, in his reply three days later, affirmed the government's commitment: "... we shall spare no efforts to mobilize all available resources...", but he pointed out that Somalia would not have had the problem if Ethiopia

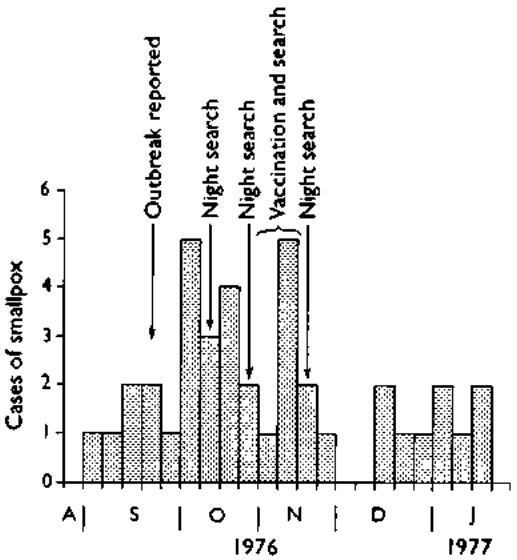

Fig. 22.5. Mogadishu: number of reported cases of smallpox, by week of onset, September 1976–January 1977.

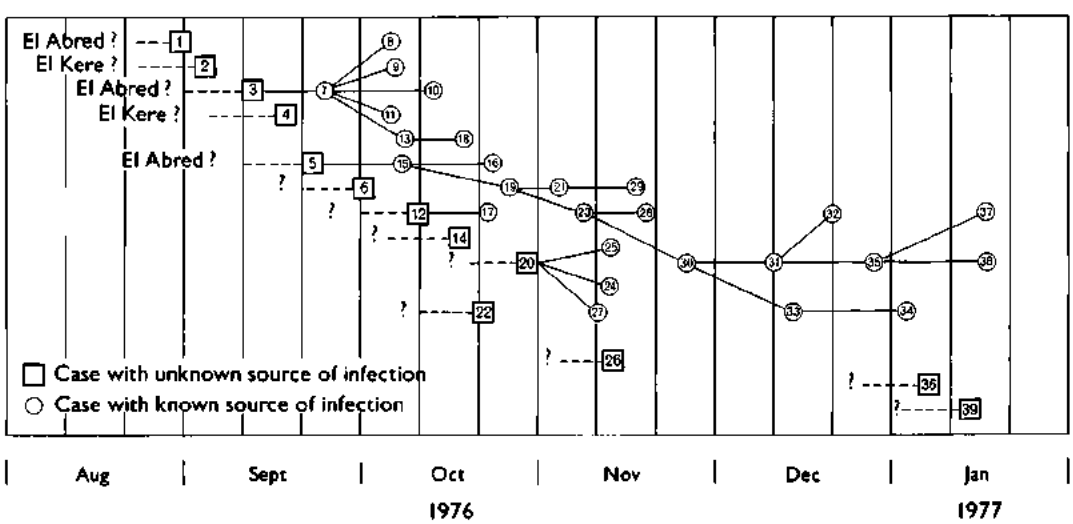

Fig. 22.6. Mogadishu: ostensible chain of transmission of smallpox, September 1976–January 1977.

had acted prudently; he requested that US$2 000 000 should be made available.

Permission to search in the 5 regions was not, however, forthcoming. It was therefore proposed that Ladnyi, at that time an Assistant Director-General of WHO, should visit Somalia early in December to discuss the problem. With Ladnyi's impending visit, permission was given for the WHO epidemiologists to make 1-day visits to each of the regions in the south; later, on 15 December, they were allowed to make such visits in the northern regions. Little could be done in the way of search during such brief visits but at least the WHO staff were thus enabled to make personal contact with the regional health authorities and to discuss the need for case detection—though everyone they spoke to denied that smallpox was present.

As a consequence of Ladnyi's visit, permission was given for WHO staff to visit the hospital regularly with Somali counterparts and to undertake investigations throughout the city. Thereafter, the transmission of smallpox in Mogadishu subsided rapidly. However, despite the visit, WHO staff were not allowed to participate in a search in other parts of the country. The Minister insisted that not less than US$2 000 000 would have to be provided before a search could begin. WHO staff considered this to be an exorbitant sum; moreover, it far exceeded the amount of money WHO then had at its disposal for smallpox eradication.

Although a national search for cases could not be undertaken, the situation appeared to improve from January to mid-March 1977. In Mogadishu, the vaccination of contacts and close neighbours of patients began to be conducted at night as well as during the day, and on 17 January 1977, the last case was reported. Repeated night searches of the entire city in January and again in February failed to detect further cases. Sanction for an organized national search was finally given on 21 January, during the fifty-ninth session of the WHO Executive Board, when the Director-General, the Director of the WHO Regional Office for the Eastern Mediterranean, Ladnyi and staff of the Smallpox Eradication unit held a private meeting with a member of the Board from Somalia. He agreed that 6 more experienced epidemiologists should be recruited immediately by WHO to serve as advisers in each of 6 regional administrative areas in southern Somalia and to help in conducting an intensive search commencing late in March. WHO agreed to provide the proposed US$350 000 in additional funds to cover expenditure on transport and supplies and local costs. It was also agreed that a special meeting would be convened in March to coordinate what was hoped would be final search activities throughout Ethiopia, Kenya, Somalia and the Sudan to confirm that eradication had been achieved.

The development of the programme in Somalia at this time was greatly facilitated by the appointment in February of a new national Smallpox Eradication Programme Manager for Somalia, the knowledgeable Dr Abdullahi Deria, who had just returned to the country from a course of study in tropical medicine. With Dr Ehsan Shafa, of the WHO Smallpox Eradication unit, he immediately set to work to draw up a search plan. So far as WHO staff then knew, only 39 cases of smallpox had been admitted to the hospital in Mogadishu, and although everyone was aware that some additional cases had occurred, it seemed unlikely that a national search would turn up large numbers of outbreaks. To facilitate the detection of cases, Dr Deria and Dr Shafa decided that, beginning in March, a reward of 200 Somali shillings (US$32) would be offered to anyone reporting a case.

WHO / E SHAFA

Plate 22.4. This man reported a case that proved to be smallpox and received the reward of 200 Somali shillings.

A disturbing event during this period was the discovery on 30 January 1977 of an outbreak in Kenya. The first case had occurred on 26 December 1976 in a Kenyan village near the Somali border, introduced by a young man returning from a religious school in Mogadishu. Shortly after becoming ill, he had returned to Somalia but no one knew where he had gone. Meanwhile, he had infected 4 other persons—his sister and her 3 children. Possible areas in and around Mogadishu were searched, but to no avail. In February, when it was learned that he might have gone to a town 80 kilometres north of the city, a Somali–WHO team investigated this area, but again, neither the patient nor any evidence of smallpox was found. It is not known what relationship, if any, the index case bore to outbreaks which were found subsequently. In part, this was because the government asked that when the 6-month national search was undertaken, cases and outbreaks which had occurred previously should not be documented.

First Coordination Meeting, March 1977

To coordinate the forthcoming intercountry search programme, Arita, with assistance from Dr Wilfred Koinange, Director of Health Services of Kenya, convened a meeting in Nairobi on 15 March 1977 of health staff from Ethiopia, Kenya, Somalia, and the Sudan. At that time, more than 2 months had elapsed since a case had last been notified. Each of the delegates reported on the nature and extent of his country's surveillance programme and expressed hope that smallpox transmission had been interrupted. Dr A. I. Idris from the Sudan, who was still sceptical, pointed out that, however satisfactory surveillance appeared to be, no link had been discovered between the outbreak in Kenya and the last outbreaks in Mogadishu. To him this indicated that other undetected cases must have occurred, and until the chains of transmission had been clearly identified efforts could not be relaxed. It was a prophetic observation.

The participants all agreed to undertake similar types of search programmes over the succeeding 6 months, involving house-to-house searches for cases and special searches among nomads, the collection of specimens from cases both of chickenpox and of suspected smallpox, and notification through WHO Headquarters in Geneva of rumours of outbreaks in other countries. Priority would be given to the Ogaden desert area. In Ethiopia a thorough search of the area would be carried out every 4–6 weeks employing 224 search workers, 16 supervisors and 4 WHO epidemiologists, provided with 18 vehicles and 2 helicopters. Kenya planned to utilize 320 public health staff and 64 locally recruited workers with 16 vehicles. In Somalia 300 search workers, 10 Somali supervisors and 7 WHO advisers with 19 vehicles would be deployed. The group agreed to meet again 6 months later to assess the situation and to decide on future action. Staff from Djibouti would also be invited to that meeting to ensure full coordination of all activities throughout the entire area.

EPIDEMIC SMALLPOX IN SOMALIA, MARCH 1977

Shortly after the Somali smallpox eradication staff returned from the Nairobi meeting, Dr Deria reported to the WHO advisers that 2 cases of smallpox had been discovered in Bakool Region, near the Ethiopian border—the first outbreak to be officially reported outside Mogadishu. A joint Somali–WHO team visited the area and was told that the first patient had been in an Ethiopian village 2 weeks earlier. Ethiopia was immediately notified but investigation revealed no evidence of smallpox in the designated village either at that time or in the past. A few days later, another case was reported from a village much further south but no source of infection could be identified. On 24 March, yet another case was reported. By mid-April there were 29 cases, and more were being discovered daily as the search programme was gradually intensified. Villagers revealed the disturbing information that smallpox outbreaks had occurred outside Mogadishu in 1976, but these had never been notified. Indeed, an outbreak of 17 cases in November and December 1976 was found to have been verified by both the regional medical officer and the WHO smallpox adviser but not officially reported.

Meanwhile, experienced WHO staff members working in India, including Dr M. K. Al Aghbari, Dr W. Hardjotanojo and Mr R. J. Hatfield, were mobilized and sent to Mogadishu in March. However, they were too few to cope with the situation. In April, Arita

A Unique Approach to Case Detection

In March 1977, the suppression of information and the concealment of cases continued to be widespread despite the new instructions of the Ministry of Health. One of the first to break this barrier was an ingenious Sudanese sanitarian, Mr Abdul Gadir El Sid, who was serving as a WHO consultant. On entering a village for the purpose of investigating suspected cases, he saw several persons with facial pockmarks suggestive of recent smallpox but was confronted with unanimous denial by the villagers that cases had recently occurred. Taking over the vehicle from his driver, he deliberately drove it into deep mud. A large crowd came from the village to help to extricate the car, and among them were 4 persons with active smallpox.

hurriedly flew from Geneva to Mogadishu, and with the agreement of the government immediately took measures to recruit 8 additional WHO epidemiologists to complement the 7 provided by the Organization who were already working there. It was the first step towards a greatly intensified effort (Table 22.5). In April alone, 157 cases were documented in more then 40 outbreaks (Table 22.6). However, the discovery of cases and the containment of outbreaks among nomads were proving to be extremely difficult. The encampments were often hard to locate in the high scrub; the groups were small, averaging no more than 30–40 persons; and less than 25% remained in a given location for more than a week. Meanwhile, search in Ethiopia was increasingly hampered by guerrilla warfare and border hostilities. The final goal of global smallpox eradication, which only weeks before had seemed imminent, was once again in doubt.

Table 22.5. Somalia: number of field staff, by category and by month, 1977

Month	Epidemiologists		Team leaders	Supervisors	Surveillance agents	Others (incl. watchguards)	Total
	WHO	National					
March	4	8	–	10	110	6	138
April	7	10	6	20	290	48	381
May	15	13	36	70	1 315	245	1 694
June	18	22	54	113	2 509	585	3 301
July	20	24	50	146	2 138	189	2 567
August	20	27	55	148	2 191	110	2 551
September	18	27	47	153	1 755	81	2 081
October	19	27	73	213	1 298	46	1 676
November	21	28	71	240	1 398	32	1 790
December	20	20	71	250	1 010	0	1 371

Table 22.6. Somalia: reported smallpox cases by month and region, 1977

Region[a]	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
Bakool	0	0	2	12	116	246	122	19	1	0	0	0	518
Bay	0	0	1	44	189	836	410	129	34	3	0	0	1 646
Galgadud	0	0	0	3	2	0	0	0	0	0	0	0	5
Gedo	0	0	0	0	3	110	70	21	12	10	2	0	228
Hiran	0	0	0	43	36	7	10	1	0	0	0	0	97
Lower Juba	0	0	0	1	2	3	0	0	0	0	0	0	6
Middle Juba	0	0	0	19	27	11	3	3	22	3	0	0	88
Mogadishu	5	0	0	2	1	1	1	0	0	0	0	0	10
Lower Shabelli	0	0	0	15	62	92	1	37	49	11	1	0	268
Middle Shabelli	0	0	0	18	198	82	55	9	0	0	0	0	362
Togdheer	0	0	0	0	0	0	0	1	0	0	0	0	1
Total	5	0	3	157	636	1 388	672	220	118	27	3[b]	0	3 229

[a] No cases were reported in Bari, Galbeed, Mudug, Nugal or Sanaag Regions.
[b] Although reported in November, all 3 cases experienced the onset of illness before 27 October.

The Emergency Programme, May 1977

In May 1977, delegates attending the Thirtieth World Health Assembly heard reports on the smallpox situation in Ethiopia, Kenya and Somalia and expressed considerable apprehension. The number of cases in Somalia was increasing each week, and with hostilities between Ethiopia and Somalia escalating, the prospects for control, let alone eradication, were not encouraging. Not only were Kenya and Ethiopia at risk of reinfection, but in the autumn, during the annual pilgrimage to Mecca, other countries would be at similar risk. Since variola minor—the predominant form—was clinically so mild, concern was expressed that pilgrims might travel to Mecca even though they were ill, and while there would spread it to other pilgrims, coming from Asia and other parts of Africa. The Health Assembly accordingly adopted a resolution (WHA30.52), which stated:

"Recognizing that, while smallpox is now reported from only a single country in north-eastern Africa, continuing smallpox transmission in that area represents considerable danger for adjacent countries owing to nomadic population movements...

"REQUESTS all Member States to continue to give financial support to the smallpox eradication programme, either through the Special Account for Smallpox Eradication of the Voluntary Fund for Health Promotion or on a bilateral basis, in order that the last known smallpox foci can be eliminated as rapidly as possible...

"URGES all governments to make full use of the expertise of international and national personnel with experience in smallpox surveillance and in containment measures as may be required effectively to interrupt transmission of the disease..."

Additional resources were urgently required but voluntary contributions from governments would inevitably take some time to become available, and WHO's funds for smallpox eradication were running low. Moreover, at least a year would elapse before vitally needed vehicles could be delivered from the factory. On 16 May WHO telephoned the Office of the United Nations Disaster Relief Co-ordinator (UNDRO) in Geneva to seek help. UNDRO indicated that it would be willing to make a world-wide emergency appeal if Somalia would officially declare the epidemic a disaster requiring the expenditure of resources beyond the country's means (WHO/SE/77.99, Hauge & Wickett). The agreement of the United Nations Development Programme's Resident Representative in Somalia that the resources requested were appropriate to the emergency was also necessary. A telex was immediately sent to Mogadishu, and on 18 May the government officially declared the situation to be a disaster and appealed for assistance. After a detailed list of urgently needed supplies had been prepared, UNDRO endorsed the request, and on 27 May issued an appeal to possible donors. Within the week, cash donations and contributions in kind amounting to some US$400 000 were received from Canada, the Netherlands, Norway, Sweden, the United Kingdom and the League of Red Cross and Red Crescent Societies. The total amount provided eventually reached US$459 750. In addition, Dr William Foege, Director of the United States Center for Disease Control, who was attending the Thirtieth World Health Assembly, offered to assign 5 epidemiologists forthwith to provide assistance over the following 3 months.

To procure and deliver 16 vehicles and tons of camping equipment, transceivers and other supplies, such as tires and spare parts, posed another problem. Two airlines which normally provided a service to Somalia suspended shipments in May because of fear of the outbreak of war. An emergency airlift was required and this was provided by Canada, Sweden and the United Kingdom. Vehicles which had already been delivered to UNICEF for an emergency reserve, plus others in the possession of the United Kingdom government and the League of Red Cross and Red Crescent Societies, were earmarked for use. Procurement and supply staff from UNDRO and WHO, working with their counterparts in various countries, hurriedly assembled materials, and in 4 special flights over the period 4–14 June the whole consignment was delivered. On 8 June the 5 epidemiologists from the USA arrived, and on 9 June the French government delivered by air 3 teams with 2 vehicles and supplies. Four persons from OXFAM, the British private charitable organization, arrived later that month. By mid-June more than 3000 national staff, primarily locally recruited workers, assisted by 23 epidemiologists working for WHO and 52 vehicles, were in the field.

Ježek and Dr B. Kříž had arrived in Mogadishu on 10 May. The former assumed the senior leadership role for WHO and the latter took immediate responsibility for the

emergency operation in Bay Region, the most affected area. On 21 May, the Somali government agreed on a detailed emergency programme to be conducted throughout the 10 regions in the south (later, as additional resources became available, the programme was extended to the northern regions). Sixteen health assistants were trained and designated as regional epidemiologists, operational offices were established in each affected district and all possible health staff were assigned on an emergency basis to search systematically for cases and to vaccinate all persons within a radius of 5–10 kilometres from the site of an outbreak. One or more WHO epidemiologists worked in each region. Regional party secretaries worked with them to mobilize party workers and assistance was offered by the Somali Women's Democratic Organization, the Somali Workers' Organization, and the Somali Youth League.

In Mogadishu the central programme office was reorganized and reinforced with a WHO administrative officer from the Bangladesh programme, a transport and supply officer and, later, a finance officer. In April, the publication of a weekly surveillance report began. Training programmes, launched in May in Mogadishu, were conducted thereafter in every region. Monthly meetings of all senior staff throughout Somalia began in June; they were attended by the Minister of Health and by Arita, who travelled every month from Geneva for the purpose.

Operations were initially concentrated in southern Somalia. Most of the outbreaks were centred in the area between the Juba and Shabelli rivers, the most fertile and heavily populated area in the country. The area was criss-crossed by watercourses which flowed briefly during the seasonal rains, only occasionally reaching the sea. The rains, from March to June, were heavy in 1977, creating large marshy areas and washing away roads. Searching the areas was difficult because of the lack of maps and the fact that half the population consisted of nomadic peoples who moved frequently over long distances through the dense scrub. Work in the field was further complicated by the need to provide tents to accommodate all but the locally hired nomads and to obtain food to supplement the limited available supplies of milk and goat meat as well as jerrycans for drinking-water. Moreover, because of the prevalence of wild animals, at least 2 persons had to travel together and construct a thorn barricade around their campsite each night. Communication between personnel in the field and the staff in Mogadishu was difficult at best, a problem which could have partly been resolved by employing transceivers. However, with the invasion of the Ethiopian part of the Ogaden desert by the Somali army only a few months away, the use of transceivers was forbidden. Except for this

Plate 22.5. **A:** Rodney J. Hatfield (b. 1949), a WHO administrative officer, established critically needed motor vehicle maintenance and repair workshops in Somalia and Bangladesh. **B:** Bohumír Kříž (b. 1936), a veteran WHO epidemiologist from the smallpox eradication programmes in Asia, assumed responsibility in May 1977 for emergency operations in Bay Region, the epicentre of the smallpox epidemic in Somalia.

Vehicle Maintenance in Somalia

The availability of serviceable vehicles was especially vital in Somalia, in which the population was sparse and distances were great. When the emergency programme began in May, only 19 vehicles were in use, 11 of which were more than 5 years old. By July, a fleet of 50 4-wheel-drive vehicles was in operation. To oversee their maintenance and repair, Mr Rodney Hatfield, a veteran of smallpox eradication programmes in India and Bangladesh, was brought to Mogadishu. A valuable paper (WHO/SE/80.155, Hatfield) documents the problems of transport operation and the solutions adopted.

An initial difficulty consisted in obtaining spare parts. This was partially alleviated when substantial stocks, consigned to WHO programmes, were found in the Mogadishu customs office; some had been left in the stores for as long as 3 years. Additional orders were placed for delivery by sea and air. They included special 10-ply truck tires which were required because of the thorn scrub and the frequency of punctures.

Until February 1978, commercial garages had repaired and maintained vehicles for a negotiated price. The expenses were reduced when a WHO workshop was established in February, but even then it proved more costly than had been expected to keep the vehicles on the road. Mr Hatfield found that the servicing of a vehicle cost US$70 per 1000 kilometres for the first 48 000 kilometres and US$120 per 1000 kilometres for the next 42 000 kilometres. Over 100 000 kilometres, the total costs of labour and spare parts began to approach the cost of the vehicle. By the time vehicles had logged 150 000 kilometres, the cost of maintenance and repair was prohibitively high, making them unacceptable for unrestricted service.

restriction, government staff supported the programme, permitted travel to any area and made adequate supplies of petrol available.

A complete search was planned to take place twice a month from May to December in all high-incidence areas, once a month in low-incidence areas, and every other month in areas thought to be free of smallpox. The search programme required ingenuity in planning if all or even most nomadic groups were to be found. Gradually, a routine was established which required, first, the preparation of a sketch-map so that specific areas with landmarks could be identified and assigned to each search group. In settled areas, conventional approaches were adopted in which workers displayed the WHO smallpox recognition card and asked about possible cases at each house and in schools, markets, health units and tea-shops. In such areas, one worker could visit from 50 to 100 houses per day. For the nomadic areas, other methods were required. The initial, and simplest, approach consisted in assigning to each area of 10–15 square kilometres a literate health worker from the region and a nomad familiar with the surroundings. By inquiring in settled villages and by sighting smoke from morning camp-fires and finding the fresh faeces of domestic animals and other tracking signs, they endeavoured to locate each nomadic group within the area. Supervision of this type of search proved difficult, however, and even for nomads who knew the area, it was not easy to locate the groups because of the high scrub and the unpredictable nomadic movements. A second approach, termed the "drop and move" method (Fig. 22.7), consisted in transporting 2-person teams to points along a road and instructing them to identify and question all groups of nomads encountered during a journey of 50–150 kilometres on foot across the desert to a known landmark. This method provided greater certainty that a geographical area had been covered, but the workers were almost as difficult to supervise. As the programme progressed, and larger numbers of staff became available, a technique called the "criss-cross" search evolved. This required teams to move each day from one landmark to another across a defined area during a 3–5-day period. The search was designed in such a way that the teams would cross each other's paths at different times. Landmark check-points (usually villages) were visited by more than one team on different days, thus permitting each team to check on the work of others.

Vaccinial immunity among nomads was often found to be as low as 10%; therefore, to

Plate 22.6. Vladimir Zikmund (b. 1925) worked as a WHO epidemiologist in many southern Indian states from 1971 to 1975 before joining the emergency effort in Somalia.

diminish the probability of continuing transmission should smallpox cases recur, vaccination was initially offered by all search teams. In most areas, it was readily accepted, but in others the nomads fled into the bush, thus precluding their being examined for possible smallpox. For this reason vaccination was suspended in some areas except when outbreaks were found. Among both Somali and WHO staff, the efficacy of combining vaccination with the search for cases was frequently debated, and the practice differed somewhat from area to area. It soon became apparent, however, that the epidemiology of variola minor in Somalia was different from that observed in other parts of the world and differed significantly from that of variola major. Outbreaks in small groups did not terminate quickly but, rather, persisted for long periods among comparatively small nomadic bands. On 5 occasions, smallpox was found to have persisted for 3 months or longer in groups of less than 100 persons

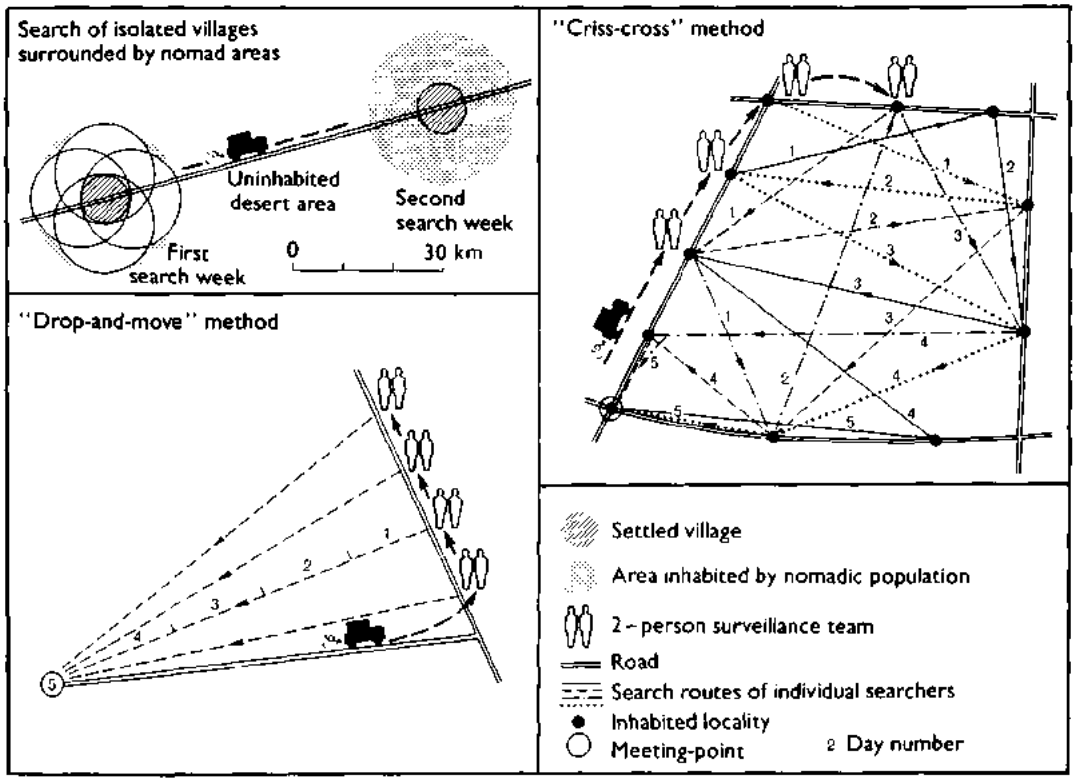

Fig. 22.7. Somalia: smallpox search methods. Surveillance workers were expected to walk 15–20 kilometres a day.

Table 22.7. Somalia: prolonged transmission of smallpox among groups of nomads

Outbreak	Population of nomadic group	Number of cases	Number of days between first and last cases
1	55	14	163
2	44	19	155
3[a]	35	24	152
4[a]	98	20	106
5	75	23	95

[a] Outbreaks 3 and 4 were interrupted by containment.

(Table 22.7). Because of the difficulties of locating such groups and keeping them under surveillance, the decision was made to vaccinate wherever a search was conducted so as to increase the overall levels of vaccinial immunity. This, it was hoped, might serve to retard or stop transmission more quickly. Vaccination scar surveys performed in the south showed levels of vaccinial immunity of 70% or higher by August 1977 and 90% or higher by September. Only 141 days after the emergency programme began, the last known case of smallpox occurred.

Outbreak-containment practices in settled areas were similar to those which had evolved during the programme in Asia. The patient was isolated, a list of village residents was compiled and all were vaccinated, and a team was posted to the village until the patient recovered in order to vaccinate visitors and to conduct continuing search and vaccination within a radius of 5–10 kilometres. Major differences of opinion arose, however, among both Somali and WHO staff as to where the patient should be isolated. Traditionally, patients in Somalia had been isolated in camps situated, in some instances, as far as 100 kilometres from their homes. Adult patients and their families, especially among the nomads, often objected to this practice; in consequence, cases went unreported and sometimes were hidden from search teams. During the early phases of the emergency programme, few of the isolation camps were well organized or provided adequate food or shelter. Accordingly, many patients who suffered from the mild illness characteristic of variola minor decided to leave the camps before recovery and, because they were inadequately guarded, did so with ease. Moreover, procedures to ensure the vaccination of family members who accompanied patients with smallpox or other skin infections were lax. As a result, the isolation camps, like hospitals in other countries, initially played an important role in disseminating smallpox.

Observations on Surveillance among Nomads

Dr B. Kříž, an epidemiologist from Czechoslovakia who had worked previously in Asia, made a number of interesting observations regarding surveillance techniques among nomads.

In bush areas in which nomads were semi-permanently settled, he discovered that they were usually easily located. Inhabitants of the nearest villages were generally well informed as to where and how many nomads were settled nearby. Village headmen, members of the village political committee and shopkeepers could provide this information. Because even relatively small areas of the bush—say, 10 square kilometres—had their own names, the nomads could be located if a map were prepared which showed the names of such places, water-holes, tall trees and roads.

In areas only temporarily inhabited during the dry season, the problem was different because the nomads were constantly on the move and there were few settled inhabitants. In places where water-holes were scarce, a well-motivated "government water-hole watchguard" was extremely useful. In some regions, however, water-holes were so numerous that water-hole surveillance was neither practicable nor useful. Market searches were also of limited value. Frequently, only female nomads visited the market but they were not easy to converse with and usually avoided giving information. In such areas, the so-called "criss-cross" technique of search (see Fig. 22.7) was essential.

To monitor nomadic movement and surveillance, it was found useful to give to the headman of a group a small WHO smallpox recognition card with the name of the place and the date when the card was given. This was widely accepted, and as its value in assessing search activities became apparent a specially designed durable card was prepared.

The alternative to isolating the patient in a special camp was to isolate him in his house, as had been the practice in Asia. In settled areas, this could be done using vaccinators as watchguards to ensure that the patient remained in the house and that all visitors were vaccinated. The task was much more difficult with nomads, who moved their camps every week or two. Moreover, the custom of visiting the sick contributed to the spread of smallpox. Hence, a special study was conducted in nomadic areas to determine what procedure would be the most culturally acceptable (Foster & Deria, 1983). It was decided that the best solution would be to construct a *haro*—a circular barrier of thorn bushes normally used to hold and protect animals at night. Accordingly, in most areas patients were isolated in a *haro*, 10–20 metres in diameter, containing a lean-to shelter and latrine. From funds provided by WHO, each patient was given 5 Somali shillings (US$0.80) a day as an incentive to remain in the shelter, and 2–4 members of the nomadic group were paid 5 Somali shillings a day to build the *haro*, to enforce isolation, to provide food and water and to vaccinate those at the encampment. When the nomads decided to move, a surveillance agent travelled with them in order to detect any additional cases and to ensure that any persons with whom they came in contact were vaccinated.

In some areas, isolation camps continued to be used but conditions in them were improved and supervision was strengthened. Patients were found to cooperate more readily if, on discharge, they were given new clothes—a practical public health measure because it permitted the old clothes to be burned, thus averting the risk of the spread of infection by fomites. Morever, as one observer noted, the new clothes served as "a moving poster" which promoted the use of the isolation camps.

The Epidemic, March to October 1977

The epidemic, first recognized in mid-March, rose to a peak in June (Fig. 22.8). Although reports had been suppressed until March, it did not appear that the smallpox

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Plate 22.7. A Somali guards the entrance to a hut in which a nomad with smallpox is isolated. These huts were built away from the encampments and enclosed by a thorn-bush barrier to keep out wild animals as well as visitors.

incidence in January and February had been high. The rise in incidence coincided with the beginning of the March rains, when nomadic movement greatly increased. A 15-day religious festival in March held in southern Bakool Region, which was attended by more than 15 000 persons, contributed to the spread. This area, with the adjacent Baidoa District in Bay Region, became the epicentre of the epidemic (Fig. 22.9) and 4% of the population contracted smallpox. The number of reported cases increased sharply in April and May, when the information spread rapidly that a reward was being given to anyone reporting an outbreak of which the authorities were unaware. In many areas, two-thirds of the outbreaks came to light in this manner, the remainder being discovered by teams during search or being reported by government officials.

The number of new outbreaks occurring during April and May far exceeded the capacity of the few advisers and an as yet untrained staff to cope with them. With the declaration of the emergency in May and the influx of personnel and resources in June, the epidemic began to come rapidly under control. As political leaders and numerous volunteers actively participated, the interval between the onset of the first case and the detection of outbreaks decreased, as did the interval between the first and last cases in the outbreaks (Table 22.8). The outbreaks were more effectively contained, and, in consequence, became smaller (Table 22.9) and

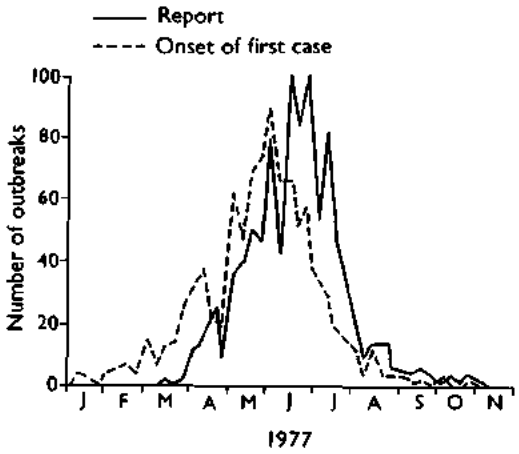


Fig. 22.8. Somalia: number of newly detected outbreaks, by week of report and by week in which the first case had onset of rash.

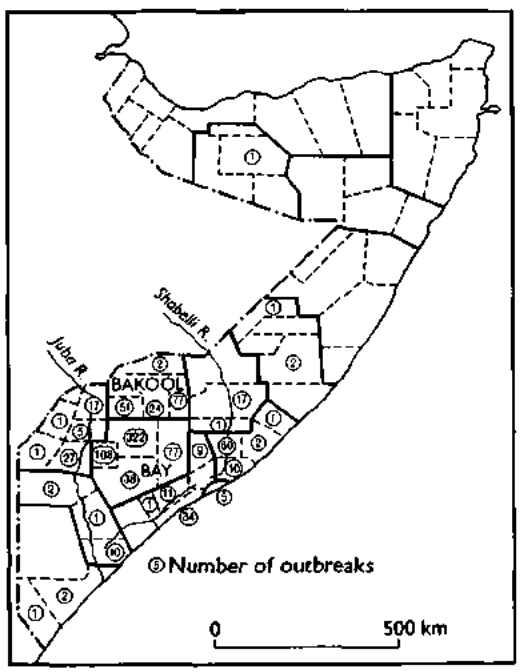


Fig. 22.9. Somalia: number of smallpox outbreaks, by district, 1977.

Table 22.8. Somalia: interval between onset of the first and last cases in the same outbreak, by month of onset, 1977

Month of onset of outbreaks	Number of outbreaks[a]				
	Total	⩽14 days	15–30 days	30–60 days	>60 days
January–March	90	17	8	30	35
April	130	62	29	31	8
May	267	145	60	55	7
June	272	208	52	10	2
July	128	104	15	8	1
August	34	26	6	2	0
September	6	2	4	0	0
October	4	4	0	0	0

[a] For which data are available.

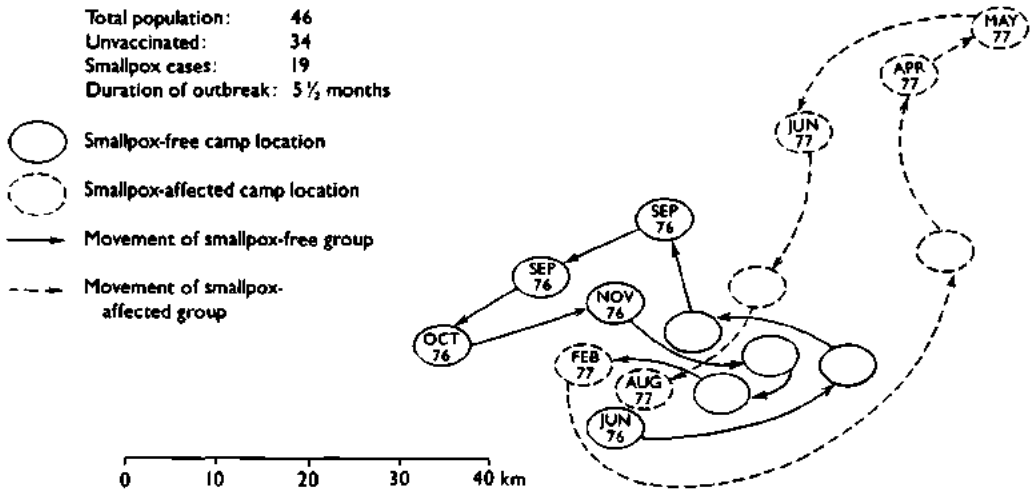
Table 22.9. Somalia: distribution of smallpox outbreaks, by size and month, 1977

Month of onset of outbreaks	Total number of outbreaks	Number of cases in the outbreak			
		1	2–4	5–9	⩾10
January–March	93	9	39	25	20
April	132	44	54	28	6
May	277	89	107	62	19
June	272	124	109	32	7
July	128	77	45	1	5
August	34	19	10	2	3
September	6	2	2	1	1
October	4	4	0	0	0

Persistent Transmission among Nomads

Dr Stanley Foster, formerly a senior WHO smallpox adviser in Bangladesh, with Mr Abdul Gadir El Sid, previously with the eradication programme in the Sudan, painstakingly documented the movements of one group of 44 nomads from June 1976 to the end of August 1977 (Foster et al., 1978). During this period, the nomads ranged over an area of about 70 kilometres by 35 kilometres (see illustration below). Only 7 members of the group had previously been vaccinated. In February 1977, the first case of smallpox occurred. The disease spread slowly among the group with only 1 or 2 cases in a generation of transmission. In all, 19 cases occurred over a 5-month period.

Somalia: Mandeelo group migration, Bakool Region, June 1976–August 1977



soon disappeared from the larger towns and villages (Table 22.10). In April 50% of the outbreaks occurred among nomads, a proportion which rose to 75% in June and to more than 90% in July. In all, 570 out of 843 outbreaks for which data are available were among nomads.

Table 22.10. Somalia: number of smallpox-affected localities, by population size and month, 1977

Month[a]	Population					Total
	<50	50–99	100–499	500–999	⩾1000	
January–March	6	3	41	15	10	75
April	7	16	49	9	16	97
May	50	51	113	9	7	230
June	82	55	77	5	4	223
July	57	30	32	2	2	123
August	9	15	8	0	0	32
September	2	2	2	0	0	6
October	2	1	0	0	1	4
Total	215	173	322	40	40	790

[a] When locality was first affected.

By late August surveys showed that 77% of the settled population and 70% of the nomads knew of the reward for reporting a case, and the epidemic had subsided to very low levels. At the end of October the last outbreak was contained. In all, 3229 cases had occurred in 947 different outbreaks. All except 5 of the cases during 1977 were outside Mogadishu. Most cases occurred in the Bay Region; few were detected outside the area between the Juba and Shabelli rivers or along their banks. Only 1 outbreak, a documented importation from southern Somalia, was discovered in the country's 6 northern regions (Fig. 22.9).

Surveillance among Nomads in Adjacent Areas of Ethiopia

With outbreaks occurring so close to the border with Ethiopia, and nomads moving freely from one country to another, surveil-

lance in Ethiopia became vitally important. Despite heightening tension between Somalia and Ethiopia and increased guerrilla warfare, Ethiopian staff continued work in the Ethiopian part of the Ogaden desert up to the end of June 1977. Between April and June, they investigated 32 rumours of cases reported by Somali staff and 136 rumours emanating from within Ethiopia. Most of these rumoured cases (96), on investigation, proved to be obvious cases of chickenpox or other skin infections. Numerous specimens were obtained but none contained variola virus. In July the Somali army occupied most of the Ogaden, and at this time surveillance by Ethiopian health staff ceased.

Surveillance in the Somali-occupied areas of the Ethiopian Ogaden provided a new challenge. Neither Somali health staff nor WHO epidemiologists were permitted into this area by the military. No surveillance was carried out for almost 2 months, but late in August an innovative "across the border" surveillance programme began. Five headquarters posts were established at different points along the border, each with Somali staff and an experienced WHO adviser: Dr M. N. El Naggar (Egypt), Mr Carl Hasselblad (USA), Dr Bert van Ramshorst (Netherlands), Dr J.-P. Ryst (France) and Dr J. S. Weisfeld (USA). Because some of the WHO staff had worked in this area previously as advisers to the Ethiopian programme, it was comparatively easy for them to recruit as supervisors and searchers the people who had previously been employed in the Ethiopian programme. With maps already available to them, it was possible to design a systematic search programme which was conducted largely on foot. Specimens were collected from all persons experiencing fever with rash and the specimens were brought back to the border posts. Between August 1977 and February 1978, 410 rumours were investigated and 151 laboratory specimens were obtained.

Independent assessment of the extent of activity of the search workers required different methods. One approach was to require each supervisor and search worker to keep a daily log-book in which he listed all the places visited and entered the full details of each person with fever and rash. The validity of the entries was then checked by other staff. On other occasions, workers were instructed to leave in each village coded WHO smallpox recognition cards. A second group visited the villages at a later date and retrieved them.

Most of the local staff in this programme performed well but some of them believed that their employment had to be justified by the discovery of rumours of smallpox cases which they would then have to investigate. Thus, throughout this period, there was a continuing and alarming flow of reports of possible cases of smallpox. Fortunately, however, an independent check could be made through an examination of the specimens obtained. None revealed the presence of smallpox.

Towards the end of 1977, concern about military security eased, but diplomatic restrictions prevented WHO staff from officially entering the areas of the Ogaden occupied by the Somali army. However, the group engaged was more concerned about smallpox than about diplomatic protocol and took it upon themselves to travel extensively throughout the Ogaden, beginning in November 1977. Areas in which outbreaks had been reported by the search workers were revisited and confirmed to be free of smallpox. This activity ceased in March 1978, when fighting again increased, causing large numbers of refugees to cross into the border areas of Somalia, many being housed in refugee camps. In a thorough investigation of these camps no one was encountered who had seen cases of smallpox since 1974 (Table 22.11).

The report describing in detail the extent of surveillance activities in the Ethiopian Ogaden during the period of occupation by the Somali army was to prove invaluable to the International Commission for the Certification of Smallpox Eradication in Ethiopia. However, even as late as October 1979, the report was considered politically sensitive and its distribution was restricted to only a few people. This caused some individuals, who had access only to publicly available

Table 22.11. Somalia: results of survey of refugee camps, February 1978

Administrative region	Number of camps	Number of people examined	% with vaccination scar	Year when smallpox was last seen
Galbeed	1	560	91	1974
Galgadud	2	1 536	58	1974
Gedo	4	8 851	66	1971–1974
Hiran	5	1 875	62	1974
Total	12	12 822	–	–

information, to question the Commission's ability to be certain of the status of the Ogaden.

The Last Smallpox Outbreak, October 1977

By the end of September 1977, the optimistic view prevailed that the discovery and containment of the world's last smallpox outbreak were at hand. On 26 September, the second intercountry coordination meeting was convened in Nairobi with representatives from Djibouti, Ethiopia, Kenya, Somalia and the Sudan. All these countries pledged a continuing intensive effort to achieve the elusive goal of eradication. At that time there were only 29 villages in Somalia known to be infected, of which 21 had active cases. Heavy rains again prohibited the use of vehicles throughout much of the area, but with large numbers of staff available it was possible to travel by foot or on camels and donkeys in carrying out the work of search and containment. Meanwhile, search in Ethiopia and Kenya continued but no cases were found.

Between 1 and 23 October, 5 more outbreaks were discovered in southern Somalia, of which 3 consisted of only a single case; the date of onset of illness in the last patient was 18 October. With a growing recognition that each outbreak contained might be the last, staff worked with an intensity never before attained. A special team arrived to make a documentary film of the programme, later released by WHO and entitled "The Search". Finally, on 31 October, yet one more case was discovered, not among nomads but in the busy regional port of Merca, a town of 30 000 inhabitants (Deria et al., 1980). The patient should have been protected by vaccination long before; after becoming ill he was in face-to-face contact with tens, perhaps hundreds, of people.

As in many other countries, the last outbreak was unusual. The patient, Ali Maow Maalin, was a 23-year-old cook who had become ill with fever on 22 October and developed a rash on 26 October. Although previously employed as a temporary vaccinator in the smallpox eradication programme and more recently as a cook in a hospital in Merca, he had never been successfully vaccinated.

On 12 October, 2 smallpox patients from a nomad encampment, some 90 kilometres from Merca, had been sent at night by vehicle to an isolation camp near the town. The vehicle stopped at the Merca hospital to seek

Plate 22.8. Participants in the second intercountry coordination meeting, Nairobi, 26–28 September 1977. *Left to right, front row:* Girma Teshome (Ethiopia), R. O. Hauge (WHO), Tesfaye Temelso (Ethiopia), Unidentified participant, M. A. Strassburg (WHO), D. W. O. Alima (Kenya), Unidentified participant; *middle row:* E. Shafa (WHO), B. O'Keefe (Kenya), P. Chasles (WHO), W. Koinange (Kenya), I. D. Ladnyi (WHO), B. Teelock (WHO), I. Arita (WHO), C. Algan (WHO), Z. Islam (WHO), N. C. Grasset (WHO); *back row:* Z. Ježek (WHO), I. O. Mwatete (Kenya), Yemane Tekeste (Ethiopia), M. Dutta (WHO), M. K. Al Aghbari (WHO), A. H. El Sayed (Sudan), A. Deria (Somalia), M. N. El Naggar (WHO), M. A. Gure (Somalia), V.J. Radke (WHO).

directions and Mr Maalin volunteered to accompany its occupants to the smallpox office, some 100 metres away. One of the 2 patients, a 6-year-old girl, was severely ill and died 2 days later. Mr Maalin was exposed for only a few minutes.

On 22 October he felt feverish and left the hospital for his home, about 200 metres away, in a densely populated area of Merca. During the next 3 days he was visited by many friends and neighbours as well as by hospital employees. He was admitted to the hospital on 25 October with a presumptive diagnosis of malaria, and received numerous visitors, walked freely through the hospital and even went outside the compound to obtain his salary payment. On the following evening he developed a rash which was diagnosed as chickenpox, and on 27 October he was discharged. Feeling ill, he remained at home although, again, he received many visitors. By 29 October he suspected that he had smallpox but, fearing to be sent to the isolation camp, did not inform the authorities. On 30 October, a male nurse at the hospital reported Mr Maalin to the regional health superintendent and to the smallpox eradication staff, who confirmed the diagnosis and sent Mr Maalin to the isolation camp. Unlike the cases of recent months, almost all of which had occurred among small isolated groups of nomads with few close contacts, Mr Maalin had been in contact with numerous people, only some of whom could be identified by name.

The hospital was immediately closed to new admissions, all patients were vaccinated and quarantined at the hospital, all health staff were vaccinated, warning signs were placed around the compound, and a 24-hour police guard was posted. Vaccination teams, consisting of 2 smallpox eradication staff, a policeman and a local political leader, listed by name and vaccinated everyone in the 50 houses surrounding Mr Maalin's home and later in the 792 houses comprising the ward in which he lived. Teams then undertook a search of the entire town each week during the succeeding 6 weeks. With police assistance, a check-point was established on the road into Merca and 3 check-points were set up on footpaths also leading into it so that all persons leaving or entering the town could be stopped and vaccinated. In all, 54 777 persons were vaccinated during the 2-week period from 31 October to 14 November. Meanwhile, meetings were held throughout Merca to inform the general public of the outbreak and to stress the need to report cases with rash and fever. The reward of 200 Somali shillings for reporting a case was widely publicized.

Efforts were made to identify all the personal contacts of Mr Maalin as well as those who had been in the same building with him at any time during his illness. In all, 91 face-to-face contacts were identified; 58 had been successfully vaccinated within the preceding 3 years; 21 had been successfully vaccinated more than 3 years earlier; and 12 had no vaccination scar. Of these 12, 6 were hospital employees, 5 were hospital patients or visitors and 1 was a personal friend. It was possible to get in touch with virtually all these people within 24 hours, although some lived as far as 120 kilometres away. They were vaccinated and placed under surveillance for 18 days, and their temperatures were taken daily in order to detect any illness as quickly as possible. Five persons under surveillance developed fever during this period and were isolated in their homes but none developed rash. Seventy other persons were identified who had been in the hospital at the same time as Mr Maalin but did not recall seeing him. All had been vaccinated previously; none developed fever during the surveillance period.

Subsequently, a house-to-house search was conducted each month for 5 months throughout the entire Lower Shabelli Region, in which Merca is situated. No further cases were found.

Finally, on 29 December 1977, 2 months after Mr Maalin had first become ill and a country-wide search for cases had been completed, it was decided that the Merca outbreak—the last one remaining on the list of pending outbreaks—could be removed from the list. Then began a 2-year period of intensive surveillance throughout the countries in the Horn of Africa to confirm that eradication had been achieved. Because of the discovery of 2 hitherto unknown foci following apparently smallpox-free intervals of 7 weeks or more (late in September 1976 and in March 1977), the surveillance was diligent. However, the Merca outbreak proved to be the last naturally occurring outbreak and Ali Maow Maalin's illness the last case.

MORBIDITY AND MORTALITY DATA, 1977

Data on the age of onset and outcome of illness are available for 3022 of the 3229 cases

Table 22.12. Somalia: reported number of cases of smallpox, by age group, 1977

Age group (years)	Cases[a]		Percentage age distribution of general population
	Number	%	
<1	47	2	4
1–4	506	17	12
5–9	560	18	15
10–14	501	17	15
15–19	406	13	14
20–29	448	15	14
30–39	259	9	11
40–49	148	5	7
50–59	78	3	4
⩾60	69	2	4
Total	3 022	100	100

[a] Details are not available for 207 other cases reported in 1977.

that occurred in Somalia in 1977. The age distribution of cases is especially interesting in that it parallels closely the age distribution of the population at large (Table 22.12). This finding might be expected in a population with little immunity either from smallpox or from vaccination. As has been noted previously, most cases occurred among nomads whose vaccinial immunity was not more than 10–20% when the epidemic began, and although the level of vaccinial immunity rose to more than 90% by September 1977, most cases had already occurred by then. Facial pockmark surveys conducted in 1978 revealed that for most southern Somali nomads smallpox was a new experience, the last large outbreaks having occurred in 1938, nearly 40 years earlier.

Only 13 deaths were recorded—a case-fatality rate of 0.4%, characteristic of variola minor. Six of the 13 individuals who died were infants less than 1 month old, 1 was a case of fetal variola, 4 were children between 1 and 6 years of age, 1 was a 49-year-old man, and 1 was a 90-year-old woman. None of them had ever been vaccinated.

CONCLUSIONS

From the time the Intensified Programme began, smallpox eradication staff had speculated as to where the last case might occur—no one had expected that it would be Somalia. Rugged, mountainous areas with a paucity of health services, such as Afghanistan or Ethiopia, or densely populated areas, such as Bangladesh or India, in which smallpox spread very rapidly, appeared to be far more likely possibilities. Somalia, with its sparse population and a more extensive network of health services than many other endemic countries, was an improbable candidate. This opinion was reinforced in 1974, when programme staff reported that the second country-wide vaccination campaign had been completed and that the total number of vaccinations performed during the two campaigns was equivalent to the population of the country.

In retrospect, the epidemic in Somalia could and should have been prevented. The first mistake was the assumption by both national and WHO smallpox eradication staff that continuing transmission of smallpox would be difficult, if not impossible, among pastoral nomads in the sparsely populated Ogaden desert. At the time, the assumption seemed reasonable. Somalia, after all, had become free of smallpox in 1962, in the absence of any national vaccination campaign, and at a time when the health services were using a poor-quality thermolabile vaccine and the numbers of people vaccinated were comparatively few. Because of this, the Ethiopian programme had concentrated its best staff and the bulk of its resources in highland areas rather than in the Ogaden. However, because of natural population growth, an augmentation of the normal nomadic population by refugees, and an increased concentration of people at feeding-camps and water-holes on account of warfare, drought and famine, the potential for continuing transmission of the virus was greater than it had been before. The second mistake was the failure to provide better WHO support to Somalia in strengthening its surveillance programme, at least after 1972, when importations began to be reported. Other activities were assigned a higher priority, in part because of the belief that transmission in Somalia could not be long sustained, especially after its extensive vaccination campaign, and in part because of the need to devote all possible resources to the intensified programmes that had begun in Asia in 1973 and in Ethiopia in 1975. The third mistake was the suppression of notifications by Somali programme staff and even the WHO smallpox adviser on the grounds that they were facing only a minor problem, which could be contained without officially acknowledging it. The staff's lack of experience in the investigation and control of outbreaks because of the long absence of

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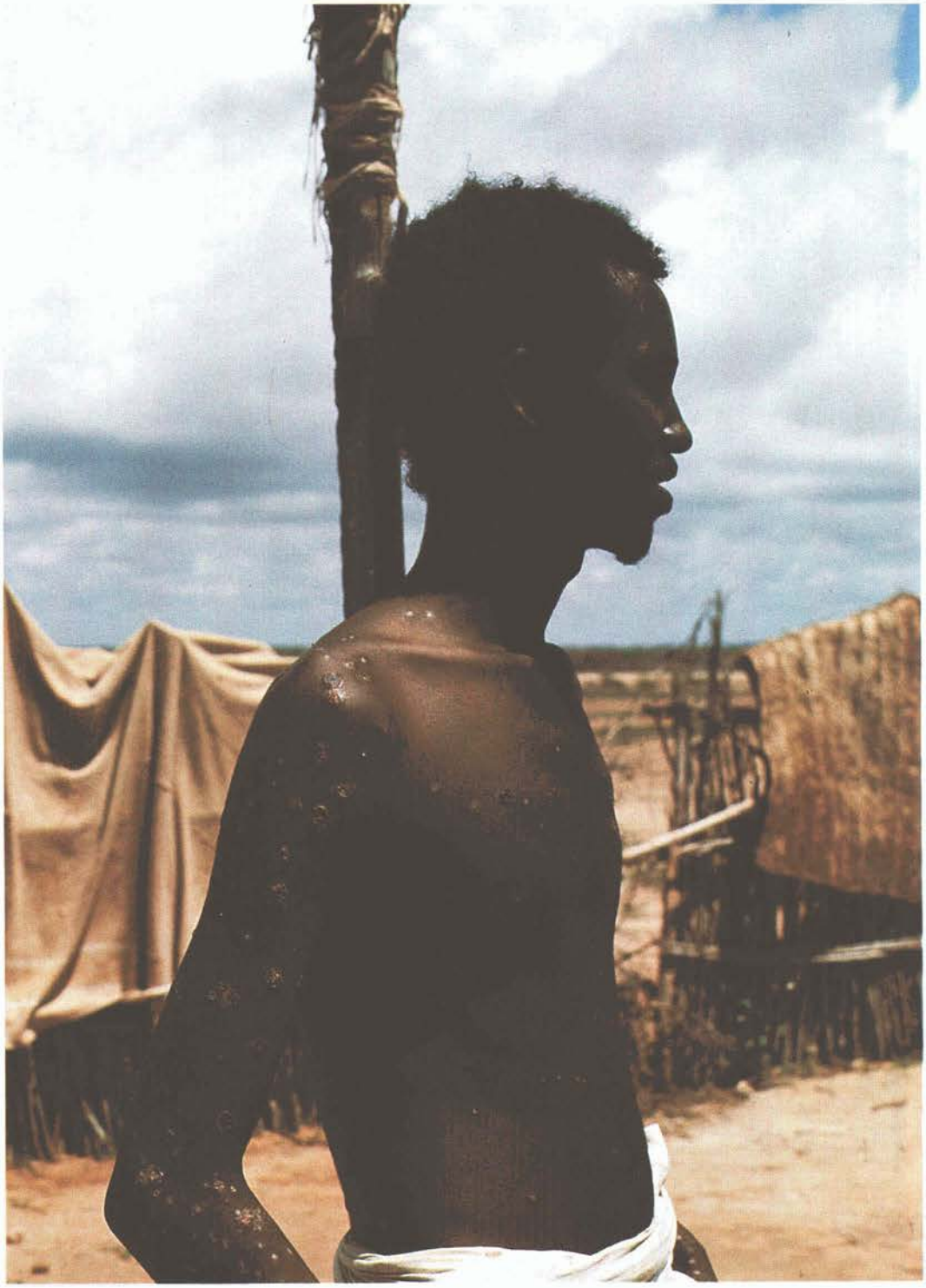
V. ZIKMUND

Plate 22.9. **A:** Airlifted vehicles being unloaded in Mogadishu for the emergency programme in Somalia in 1977. **B:** Somali search teams inquiring for rumours of possible cases of smallpox.



WHO / J. F. WICKETT

Plate 22.10. Ali Maow Maalin, the last case of naturally occurring smallpox in the world, developed a rash on 26 October 1977, in the town of Merca in Somalia.

endemic smallpox, coupled with its inability to request assistance in a situation that had not been reported, permitted a localized problem to grow into a major epidemic. The outbreak was centred in an area which, through resettlement and agricultural development, had become steadily more populated. Few cases of smallpox had occurred in the area for perhaps 40 years and an ineffective vaccination campaign, inadequately assessed, had reached only a small proportion of the inhabitants.

When the problem was finally acknowledged and an emergency declared, only 141 days were to elapse until the last case was detected and the outbreak contained. The emergency programme, conducted under the most difficult conditions, was as well executed as any national plan of operations in the Intensified Programme. A determined Somali staff aided by experienced WHO advisers worked day and night, drawing on the experience of 10 years of field activities and motivated by the imminence of the ultimate goal of global eradication. And so the final chapter was written: Ali Maow Maalin represented the last case of smallpox in a continuing chain of transmission extending back at least 3000 years.

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CHAPTER 23

SMALLPOX IN NON-ENDEMIC COUNTRIES

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INTRODUCTION

In the preceding 11 chapters we have systematically reviewed the elimination of smallpox from the 31 countries in which it was endemic in 1967 and 2 other countries (Botswana and the Sudan) in which endemicity was re-established after 1967. Because smallpox was endemic in many parts of the world in the 1960s and early 1970s, cases continued to be imported into smallpox-free countries. The annual numbers of smallpox cases in most of the larger countries between 1920 and 1958 are tabulated in Chapter 8. The year in which smallpox was last endemic in each of these countries is indicated in the tables; cases occurring after that year were due to importations. This chapter is con-

Table 23.1. Annual numbers of importations of smallpox into industrialized countries, 1959-1978

Year	Europe[a]			Canada	Japan
	Source country known	Source uncertain	Laboratory-associated		
1959	4[b]	1	0	0	0
1960	1	0	0	0	0
1961	10	0	0	0	0
1962	4	0	0	1	0
1963	2	1	0	0	0
1964	0	0	0	0	0
1965	1	0	0	0	0
1966	0	0	1	0	0
1967	4	0	0	0	0
1968	2	0	0	0	0
1969	1	0	0	0	0
1970	1	0	0	0	0
1971	0	0	0	0	0
1972	1	0	0	0	0
1973	1	0	1	0	1
1974	0	0	0	0	1
1975	0	0	0	0	0
1976	0	0	0	0	0
1977	0	0	0	0	0
1978	0	0	1	0	0
Total	32	2	3	1	2

[a] Thirteen countries; see Table 23.2.
[b] One outbreak in the Federal Republic of Germany started in 1958 but continued into 1959.

cerned with a more detailed description and analysis of outbreaks of smallpox that occurred in industrialized non-endemic countries after 1958, and in non-endemic countries of Africa, South America and Asia after 1966, when reasonably complete information first began to be compiled.

In the industrialized countries a total of 37 outbreaks due to importations from endemic areas were reported between 1959 and 1974: 34 occurred in 13 countries of Europe, 1 in Canada, and 2 in Japan (Table 23.1). In addition to importations by infected persons, there were 3 laboratory-associated outbreaks in the United Kingdom between 1966 and 1978. These are comparable to importations from endemic countries in that they were introductions of smallpox infection into a smallpox-free country; they are described in the last section of this chapter.

A notable feature of this period, compared with earlier times (see Chapters 5 and 8), was the absence of transfers of smallpox between the Eastern and Western Hemispheres, and the rarity of intercontinental importations other than from the Indian subcontinent to Europe (Fig. 23.1). This is surprising, in view of the vast volume of international traffic (4 million air passengers in 1948, 46 million in 1966, and over 400 million in 1975) and the much greater speed of travel by air than by sea.

As the Intensified Smallpox Eradication Programme proceeded, more detailed information was collected about cases throughout Africa, South America and Asia, and as a result of this effort, many outbreaks were recognized which were due to transfers across national boundaries in each of those continents. Most of these importations were contained, but some had serious consequences, leading to the re-establishment of endemic smallpox in the Sudan (1968), Botswana (1971), Bangladesh (1972) and Somalia (1976). An importation from Afghanistan into Iran in 1970 led to a large epidemic which was not terminated until 1972, and spread from Iran to Iraq, then to the Syrian Arab Republic, and from Iraq to Yugoslavia.

Excluding the laboratory-associated incidents, the 34 outbreaks in Europe produced 573 cases, of which 90 were fatal. Although the number of cases was extremely small compared with the number occurring in the endemic countries (perhaps some 50 million cases annually in the mid-1950s), health officers and the general public in the industrialized countries feared smallpox more than any other of the diseases then primarily indigenous to the developing countries.

Importations into Europe and Japan did not cease until 1974, when smallpox had been eliminated from most countries of Africa, from Indonesia, and from large areas of India and Pakistan, including most of the larger cities.

CRITERIA FOR DEFINING NON-ENDEMIC COUNTRIES

Apart from the industrialized countries, in which importations had been recognized as such from the 1940s or earlier, few efforts were made until 1967 to classify countries as having endemic smallpox or as being smallpox-free. All countries, by international convention, were supposed to report the occurrence of cases of smallpox promptly to WHO, but not all did so, nor were the reports that were received investigated to determine their validity. With the establishment of the Intensified Smallpox Eradication Programme, a deliberate attempt was made to distinguish countries in which smallpox was endemic from those that were free of the disease. Many

errors in reporting the existence of smallpox, and many instances of failure to report the disease, were discovered. After considerable inquiry, 31 countries or territories were eventually categorized as harbouring endemic smallpox in 1967 (see Chapter 10).

Between 1959, when the global smallpox eradication programme began, and 1967, a number of countries of Africa, South America and Asia which were thought to be non-endemic reported a few cases each year—too few to represent accurately an endemic situation with continuing transmission. Before 1967 few of these outbreaks had been further investigated, and it was impossible to determine whether they were due to occasional importations or represented underreported endemic smallpox, or, indeed, whether they were fictitious events reported as a result of clerical or diagnostic error.

Because of uncertainty as to whether countries in Africa, South America and Asia were indeed free of smallpox, and because reporting had been unsatisfactory and importations had rarely been fully documented, discussion of importations into these countries will be brief, and restricted, for the most part, to the period after 1967.

THE SIGNIFICANCE OF SMALLPOX IN NON-ENDEMIC COUNTRIES

Two aspects of smallpox in non-endemic countries were relevant to the global strategy of smallpox eradication: the actions taken by the countries themselves and those taken by WHO.

Actions Taken by the Non-endemic Countries

Before about 1970, almost all industrialized countries regularly vaccinated a large proportion of their population and enforced the requirement stipulated in the International Health Regulations that international travellers should hold valid certificates of vaccination. These measures were pursued with varying degrees of diligence in different countries. In the USA, for example, most children were required to show evidence of vaccination at school entry and the vaccination rate in the population as a whole exceeded 95%. In the United Kingdom vaccination was encouraged but not enforced, except for international travellers, and only about 60% of the population were vaccinated.

Vaccination certificates

Many countries placed considerable reliance on the examination of certificates of vaccination, spending much money on checking them and complaining about falsified certificates. However, there were several deficiencies in the certification system. For example, vaccination certificates were regularly examined at most—but not all—European airports. This was less of a problem in Canada and the USA, in which airport health officials were rather more rigorous in asking all arriving passengers where they had been in the preceding 14 days and requiring a valid vaccination certificate from all those who had been in a smallpox-endemic country during this period.

With regard to vaccination certificates, there was much discussion of the need to examine the results of vaccinations 7–9 days later to confirm whether these had been successful, and to require a repeat vaccination if they had not. Few appreciated that much of the vaccine used, especially in endemic countries, was of low potency, and that the failure of a first attempt often resulted in a second vaccination with equally poor vaccine. However, certificates did not require that the results of a second primary vaccination should be examined.

The principal value of vaccination certificates probably lay in encouraging most travellers to be vaccinated before they left their own country. Most intercontinental travellers were from non-endemic countries, and although they were in fact responsible for the majority of importations into European countries (see the next section), the number of incidents might have been much higher had there been no requirement for vaccination certificates.

Control of outbreaks

In accordance with the philosophy of smallpox control then prevalent (see Chapter 9), industrialized countries in the 1950s and early 1960s usually responded to the discovery of an importation of smallpox by mounting a large vaccination campaign, in parallel with efforts to identify contacts and vaccinate and isolate them. For example, in the outbreak

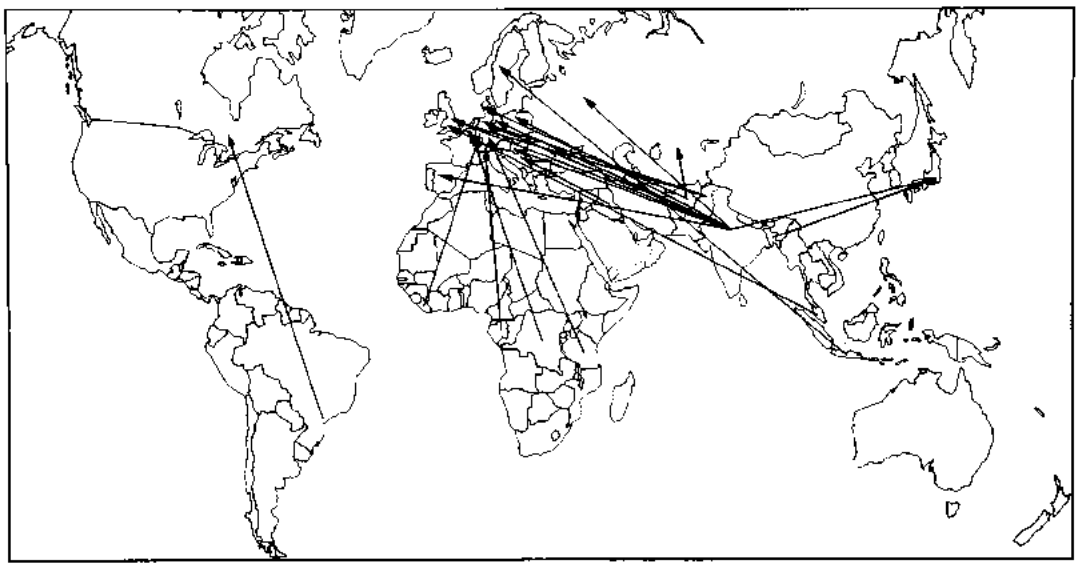

Fig. 23.1. International transfers of smallpox from Africa and Asia to Europe and Japan, 1959–1974, and from Brazil to Canada in 1962. In several cases one arrow represents several transfers, e.g., between India and the Federal Republic of Germany and between Pakistan and the United Kingdom.

which followed an importation into Stockholm, Sweden, in 1963 and caused 27 cases of smallpox and 4 deaths, some 300 000 persons were vaccinated in a period of a few weeks, with 1076 reported complications, of which 77 were serious (Ström & Zetterberg, 1966).

In the late 1960s and 1970s, when surveillance and containment were accepted as the best method of smallpox control, mass vaccination campaigns were rarely undertaken. One exception was the mass vaccination programme undertaken during the large outbreak in Yugoslavia in 1972. Earlier, in 1970, the Federal Republic of Germany had considered mass vaccination when an outbreak occurred at Meschede Hospital, but had been persuaded by WHO not to implement this operation, on the grounds that it was unnecessary and would be costly and likely to result in many complications.

The two countries in Europe with the most importations, the Federal Republic of Germany and the United Kingdom (see Table 23.2), maintained special hospitals for the isolation of smallpox patients, which were held on stand-by in case of a possible outbreak of the disease. The last of these hospitals in the United Kingdom, the Catherine-de-Barnes Isolation Hospital near Birmingham, was not closed until 1985. At the 1976 Winter Olympic Games in Austria, a special building with 8 beds was set aside for use as a smallpox hospital in the event of an outbreak and was identified as such.

Clearly, the health authorities of the industrialized countries remained highly apprehensive of the danger of smallpox, a view shared by the general public. This was evident in the Meschede outbreak, during which motor vehicles bearing a Meschede numberplate sometimes had difficulty in obtaining petrol from garages in other parts of the Federal Republic. As late as 1978, after the laboratory-associated outbreak in Birmingham, England, health authorities in 8 countries demanded valid vaccination certificates for a period of many weeks from all passengers arriving from the United Kingdom, and the authorities in another 6 countries required them from passengers who had been in Birmingham in the previous 14 days.

The attitude to importations in developing countries was not so rigorous, except in those in which a recent campaign had led to the eradication of the disease and thus to a heightened sense of the risk of importation. In the developing countries, many importations resulted in substantial outbreaks and on several occasions to the re-establishment of endemicity.

Actions Taken by WHO

Although the health authorities of the industrialized countries were responsible for controlling any importations, after the establishment of the Intensified Smallpox Eradication Programme WHO took several steps to assist them. An emergency supply of vaccine was held in Geneva, and the health authorities of all countries were notified that members of the WHO Smallpox Eradication unit were prepared to travel at short notice to any country requesting assistance. This rarely proved necessary, but the Smallpox Eradication unit maintained close telephone contact with the relevant health authorities until the emergency was over. However, Henderson and a WHO consultant, Dr Paul Wehrle, assisted in the investigation of the unusual outbreak at Meschede (see Chapter 4); vaccine and WHO technical assistance were supplied to Yugoslavia in 1972; and in 1978 Dr Joel Breman, then a member of the unit, visited the United Kingdom to take part in the inquiry into the laboratory-associated outbreak in Birmingham.

Assistance was also provided by WHO after importations of smallpox into Bangladesh, Botswana, the Gulf states, and the Sudan. Finally, reports of smallpox in non-endemic countries which reached WHO through the reporting system were always investigated to ascertain whether or not they were due to misdiagnosis or to clerical error. Such investigations had been conducted throughout the programme and even after eradication, during the operation of the international rumour register (see Chapter 28).

The *Weekly epidemiological record* was a very useful means for the prompt dissemination of information about smallpox (see Chapter 10); it was widely distributed by WHO to Member States, particularly to their epidemiologists and port and airport health services. In 1968, a large number of reprints of an article by Dumbell (1968), "Laboratory aids to the control of smallpox in countries where the disease is not endemic", was given special distribution to Member States. Also in 1968, the Smallpox Eradication unit invited Dr Thomas M. Mack, then an epidemiologist at the United States Communicable Disease Center, to WHO Headquarters, where he reviewed importations of smallpox into Europe; his paper, "Smallpox in Europe, 1951–1971" (Mack, 1972), was the first comprehensive analysis of the epidemiological pattern of smallpox importations into non-endemic countries.

SMALLPOX IN EUROPE, 1959–1978

Over a period of 20 years, from 1959 to 1978, 13 European countries—about half the larger countries of the continent—reported the occurrence of cases of smallpox. Excluding laboratory-associated outbreaks, which are discussed at the end of this chapter, there were 34 importations from endemic countries, and on 4 occasions the disease spread to neighbouring countries (Table 23.2).

Outbreaks occurred in Europe each year from 1959 to 1973, except 1964, 1966 and 1971, with the largest numbers in 1961, 1962 and 1963. In all, 573 cases were recorded, including the imported (index) cases. The largest outbreaks consisted of 175 cases in Yugoslavia and an associated case in the Federal Republic of Germany (1972), 99 cases in Poland and an associated case in the German Democratic Republic (1963), 47 cases in the United Kingdom (1962), and 46 cases in the USSR (1959–1960). The other 30 introductions caused single-case outbreaks on 14 occasions and outbreaks of 2–33 cases on 16 occasions. Although two-thirds of the outbreaks led to no more than 5 cases, their impact on the communities in which they occurred was out of proportion to the real risk; cases always made the headlines in the newspapers, many persons sought vaccination, and in the larger outbreaks mass vaccination campaigns were urged or undertaken.

The Federal Republic of Germany and the United Kingdom, which together accounted for 19 of the importations from the endemic countries during this period, were the most frequently affected, in part because of the more frequent travel between them and the Indian subcontinent.

Sources of Importations

Asian countries were the source of infection for 28 of the 34 introductions from outside Europe; in only 5 instances was infection brought from Africa, once each from Gabon, Liberia and the United Republic of Tanzania, and twice from Zaire. The Indian subcontinent was the principal source of importations, 14 coming from India and 8 from Pakistan.

As the smallpox eradication programmes progressed in the endemic countries, introductions of smallpox into Europe became less and less frequent—23 in 1959–1963, 7 in 1964–1968 and 4 in 1969–1973—in spite of the increase in the volume of air travel over this period.

Twenty-seven of the 29 importations from overseas for which data are available were associated with air travel, but none resulted from transmission on an aeroplane; all the infected persons were in the incubation period or the prodromal phase of the disease, when virus was not transmitted. The 2 outbreaks in 1962 in which the index case travelled by ship were recognized during the voyage or when the ship docked, as the patients arrived with fully developed signs and symptoms. On one occasion only (No. 33 in Table 23.2) was the index case known to have travelled by bus, and the prodromal symptoms of smallpox, which were taken to be due to fatigue from the long journey, did not develop until after the arrival of the person concerned in Yugoslavia.

In 4 instances, cases were imported from one European country into another. A single case that occurred in Schaffhausen in Switzerland in January 1962 was probably infected in Düsseldorf, in the Federal Republic of Germany, at the end of December 1961 (No. 12 in Table 23.2). In 1970, a case in Tromsö in Norway had been exposed to one in Denmark (No. 32), and a case occurred in the Federal Republic of Germany in a man who had been exposed during the epidemic in Yugoslavia in

Table 23.2 Importations of smallpox into Europe by travellers, 1959–1974

Serial number	Date of occurrence		Importing country	First affected locality	Country of origin	Means of transport of index case	Numbers of	
	Year	Month					Cases	Deaths
1	1958–59	Dec.	Federal Republic of Germany	Heidelberg	India	Air	20	2
2	1959	March	United Kingdom	Liverpool	?	?	1	0
3	1959	April	German Democratic Republic	Berlin	India	Air	1	0
4	1959	July	USSR	Termez	Afghanistan	Land	1	0
5	1959	Dec.	USSR	Moscow	India	Air	46	3
6	1960	Oct.	United Kingdom	London	Malaysia	Air	1	0
7	1961	Jan.	Spain	Madrid	India	Air	17	3
8	1961	March	Federal Republic of Germany	Ansbach	India	Air	4	1
9	1961	April	USSR	Moscow	India	Air	1	0
10	1961	Oct.	Belgium	Brussels	Zaire	Air	1	1
11	1961	Oct.	USSR	Kirovabad	Afghanistan	Land	1	0
12	1961	Dec.	Federal Republic of Germany	Düsseldorf	Liberia	Air	6[a]	2
13	1961	Dec.	Federal Republic of Germany	Lammersdorf	India	Air	33	1
14	1961	Dec.	United Kingdom	Bromwich	Pakistan	Air	2	0
15	1961	Dec.	United Kingdom	London	Pakistan	Air	3	1
16	1961	Dec.	United Kingdom	Bradford	Pakistan	Air	14	6
17	1962	Jan.	United Kingdom	Birmingham	Pakistan	Air	1	0
18	1962	Jan.	United Kingdom	Cardiff	Pakistan	Air	47	19
19	1962	March	Poland	Gdansk	India	Sea	33	0
20	1962	Aug.	United Kingdom	London	India	Sea	3	0
21	1963	March	Sweden	Stockholm	Asia (?Indonesia)	Air	27	4
22	1963	May	Poland	Wrocław	India	Air	100[b]	7
23	1963	Aug.	Switzerland	Zürich	Gabon	Air	1	0
24	1965	Oct.	Federal Republic of Germany	Kulmbach	United Republic of Tanzania	Air	2	0
25	1967	Feb.	Federal Republic of Germany	Regensburg	India	Air	2	0
26	1967	March	Czechoslovakia	Prague	India	Air	1	0
27	1967	March	Federal Republic of Germany	Hanover	India	Air	1	0
28	1967	Oct.	United Kingdom	London	Pakistan	Air	2	0
29	1968	Feb.	United Kingdom	London	Pakistan	Air	1	0
30	1968	Sept.	Belgium	Namur	Zaire	Air	1	0
31	1969	Dec.	Federal Republic of Germany	Meschede	Pakistan	Air	20	4
32	1970	Aug.	Denmark	Skodsborg	Afghanistan	Air	2[c]	1
33	1972	Feb.	Yugoslavia	Kosovo	Iraq	Land	176[d]	35
34	1973	Feb.	United Kingdom	London	India	Air	1	0
							Total: 573	90

[a] One case in Switzerland.
[b] One case in the German Democratic Republic.
[c] One case in Norway.
[d] One case in the Federal Republic of Germany.

1972 (No. 33). The large outbreak in Poland in 1963 (No. 22) was probably responsible for a single case in the German Democratic Republic later that year.

Nature of Index Cases

The index case in importation No. 4 (Table 23.2) was said to have been infected with virus transmitted from Afghanistan on a carpet, but little additional information is available; all other outbreaks were known to be due to the entry of infected persons. Of the other 31 importations into Europe (details are lacking for No. 2 and No. 11), 20 of the index cases occurred in Europeans who had recently visited smallpox-endemic areas. Their occupations varied; among them were 4 physicians and 4 engineers or electricians. Only 11 index cases (7 adults and 4 children) were nationals of an endemic country: 7 were Pakistanis and 4 were Indians and all of them were visiting relatives or friends in the United Kingdom, except for an Indian visiting the Federal Republic of Germany.

Among those importing smallpox, the proportion of males to females was 26 to 5. Twenty-four were adults; the youngest was a 6-month-old baby infected in Zaire (No. 30 in Table 23.2) and the oldest a Swiss nurse aged 70 years who was infected in Gabon (No. 23).

Only one-third of the index cases gave histories of apparently satisfactory smallpox vaccination. In spite of the availability of potent vaccine and the concern of health officers in European countries regarding importations of smallpox, case histories revealed that most of the Europeans responsible for importations were not well protected when visiting endemic countries. It was estimated that about 70% of the importations resulted from unsatisfactory revaccinations, for which poorly kept liquid vaccine seemed mainly responsible. Throughout the global eradication programme health officials expressed great concern about forged vaccination certificates and focused much of their attention on this matter, but it probably played a fairly marginal role, only a few migrants from the Indian subcontinent being implicated.

Of 28 index cases who arrived from abroad by plane, only 5 had signs of disease on arrival, including an acne-like rash and lesions on the lips. Six arrived in the prodromal, influenza-like stage and the remaining 16 landed apparently healthy; it was impossible to identify any of these cases on arrival. One-third of those who were incubating smallpox

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Plate 23.1. Checking vaccination certificates at Moscow Airport. This procedure caused expense and delays at every international airport until smallpox had been eradicated throughout the world.

Table 23.3 Delays in notification and the extent of spread of smallpox in 30 outbreaks in Europe, 1959–1973

Time-lag[a] (days)	Number of importations	Total number of cases	Average number of cases per importation
0–7	16	87	5.4
8–14	5	44	8.8
15–21	4	63	15.8
≥ 22	5	339	67.8
Total	30	533	17.7

[a] Interval between the date of onset of fever in the first case and date of notification to the health service.

fell ill within 3 days of their arrival and the other two-thirds by the end of the first or the second week after arrival. Recognition of the disease and its notification were often delayed, since the doctors who saw the cases often did not suspect smallpox and were usually unfamiliar with its clinical picture.

Delays in Notification

Of 30 importations for which data are available, 21 were recognized as smallpox within 2 weeks of the arrival of the index cases, indicating that the importations were discovered within one incubation period of the first generation of the cases (Table 23.3). On 5 occasions (No. 12, No. 13, No. 21, No.22 and No. 33 in Table 23.2), delays of more than 3 weeks (range, 22–42 days) occurred before the recognition of smallpox. All these outbreaks resulted in serial transmission for 3 or more generations (see Table 23.4). Clearly, the longer the delay in discovery, the greater was the number of cases that occurred. Sometimes, however, the index case was promptly recognized but a first generation case was missed, as in importation No. 18, in Cardiff, Wales, in which the index case was correctly diagnosed within 4 days of the onset of fever, but a female first-generation patient was not discovered for 20 days; 47 cases occurred in this outbreak, despite early detection of the index case.

Transmission from Imported Cases

In 14 of the 34 importations into Europe there were no secondary cases (Table 23.4). Of 20 importations in which transmission occurred, 12 resulted in 1 or 2 indigenous generations and 5 in 3 or 4 generations; in only 3 importations were there more than 5 generations of transmission. Except for the last-mentioned outbreaks, containment measures were successful in interrupting transmission within about 2 months.

Seasonal effects

Although importations occurred at all times of the year, they were more numerous in the winter and spring (Table 23.5), the usual periods of seasonal increase in smallpox incidence in the endemic areas of the Northern Hemisphere from which most importations originated. The importations at this time of the year usually caused considerably larger outbreaks than those in the summer and autumn, showing that the temperate countries of Europe were also subject to seasonal influences.

Cases infected in Europe

Of the 573 known cases, 35 were index cases infected outside Europe, including 3 cases on board ship in outbreak No. 19. Of the 537 indigenous cases, 277 (52%) were infected in health establishments or during the course of medical or nursing duties (Table 23.4); 57 (21%) of them were fatal. The other 261 cases resulted from intimate contact with cases in affected households or from casual contacts in institutions such as schools or factories. Although most cases in Europe were cared for in well-equipped hospitals, these institutions played an important role in the further dissemination of smallpox and posed a real risk for other patients as well as staff. The routine vaccination of hospital staff was recommended in Europe and North America, but it was rarely carried out satisfactorily. Most cases occurred among young medical professionals, nearly 20% of whom had never been successfully vaccinated. In contrast, cases among hospital patients and visitors occurred most frequently in young children and aged persons. A few cases were reported in seamen and port employees, as in outbreak No. 19. A Czechoslovak Airlines navigator who contracted smallpox (No. 26) was infected during his stay in Bombay, not on his plane.

Case-fatality rates

There had been several importations of variola minor into Europe during the first half of the 20th century, but all importations

Table 23.4 Europe: smallpox outbreaks by generation

Serial number	Year	Importing country	Number of imported cases	Indigenous generation						Total number of cases	Infections acquired in hospitals or by other health staff	
				1	2	3	4	5	6		Number of cases	Number of deaths
1	1958	Federal Republic of Germany	1	10	6	3	0	0	0	20	19	2
2	1959	United Kingdom	1	0	0	0	0	0	0	1	0	0
3	1959	German Democratic Republic	1	0	0	0	0	0	0	1	0	0
4	1959	USSR	a	1	0	0	0	0	0	1	0	0
5	1959	USSR	1	19	23	3	0	0	0	46	19	1
6	1960	United Kingdom	1	0	0	0	0	0	0	1	0	0
7	1961	Spain	1	13	3	0	0	0	0	17	13	2
8	1961	Federal Republic of Germany	1	2	1	0	0	0	0	4	1	0
9	1961	USSR	1	0	0	0	0	0	0	1	0	0
10	1961	Belgium	1	0	0	0	0	0	0	1	0	0
11	1961	USSR	1	0	0	0	0	0	0	1	0	0
12	1961	Federal Republic of Germany	1	2	1	2	0	0	0	6	2	2
13	1961	Federal Republic of Germany	1	3	20	6	3	0	0	33	19	1
14	1961	United Kingdom	1	1	0	0	0	0	0	2	1	0
15	1961	United Kingdom	1	1	1	0	0	0	0	3	0	0
16	1961	United Kingdom	1	10	3	0	0	0	0	14	13	5
17	1962	United Kingdom	1	0	0	0	0	0	0	1	0	0
18	1962	United Kingdom	1	1	6	18	1	18	2	47	26	16
19	1962	Poland	3	11	19	0	0	0	0	33	0	0
20	1962	United Kingdom	1	2	0	0	0	0	0	3	0	0
21	1963	Sweden	1	4	10	7	1	2	2	27	15	2
22	1963	Poland	1	2	4	26	44	20	3	100	46	4
23	1963	Switzerland	1	0	0	0	0	0	0	1	0	0
24	1965	Federal Republic of Germany	1	1	0	0	0	0	0	2	0	0
25	1967	Federal Republic of Germany	1	1	0	0	0	0	0	2	0	0
26	1967	Czechoslovakia	1	0	0	0	0	0	0	1	0	0
27	1967	Federal Republic of Germany	1	0	0	0	0	0	0	1	0	0
28	1967	United Kingdom	1	1	0	0	0	0	0	2	0	0
29	1968	United Kingdom	1	0	0	0	0	0	0	1	0	0
30	1968	Belgium	1	0	0	0	0	0	0	1	0	0
31	1969	Germany	1	17	2	0	0	0	0	20	19	4
32	1970	Denmark	1	1	0	0	0	0	0	2	0	0
33	1972	Yugoslavia	1	11	140	24	0	0	0	176	84	18
34	1973	United Kingdom	1	0	0	0	0	0	0	1	0	0
Total			35	114	239	89	49	40	7	573	277	57

[a] Infection said to have been transmitted on a carpet.

after 1959 were of variola major. The overall case-fatality rate of 16% (see Table 23.2) was of about the same magnitude as that in endemic countries, the deaths occurring primarily in unvaccinated infants, in persons with contraindications to routine vaccination, and in older patients who had been vaccinated many years earlier.

The extent of individual outbreaks in Europe

Except for a few outbreaks, smallpox importations into Europe did not produce large numbers of cases, reaching double figures in only 11 outbreaks, even though some outbreaks were not discovered for as long as 3 weeks after the onset of illness in the first case (Table 23.3). Forty per cent of the importations caused no further transmission. After 1963, only 2 outbreaks occurred in which there were more than 2 cases, and both were associated with unusual circumstances: severe cough and the aerosol spread of virus in outbreak No. 31 (Meschede), and spread in Yugoslavia in one of the country's least developed areas, involving an unrecognized case in a man who was moved from hospital to hospital (No. 33). The fact that there was not greater spread can be attributed in part to the prompt isolation of patients at home or in hospital and to the generally rapid and effective application of control measures.

Especially after 1967, however, smallpox importations into Europe received extensive press, radio and television coverage. Despite the prompt measures usually taken by the public health authorities, the deep-rooted if sometimes unfounded fears of the population were difficult to quell. Several countries suffered considerably in consequence. For

WHO

Plate 23.2. Some non-endemic countries kept special hospitals ready for the isolation of patients in case smallpox was imported. Sign on a public road in Yorkshire, England, during an outbreak of smallpox in 1953.

example, in the first few days after the recognition of the large outbreak in Yugoslavia, the country was in turmoil: people were afraid to visit public places until they and their families had been protected by vaccination; trucks carrying market products from affected areas were turned back; tourist bookings were cancelled; and some countries closed their borders and advised their nationals not to visit Yugoslavia. Only after a steady flow of epidemiological information and surveillance data had reassured neighbouring countries were the last of the restrictions on trade and travel dropped, some 12 weeks after the beginning of the outbreak.

Table 23.5 Europe: seasonal influence on the numbers of importations of smallpox and the size of outbreaks following importations

Month	Number of importations	Total number of indigenous cases[a]	Average number of indigenous cases
January	3	62	20.7
February	4	176	33.0
March	6	59	9.8
April	2	0	0
May	1	99	99[b]
June	0	–	–
July	1	0	–
August	3	3	1.0
September	1	0	0
October	5	2	0.4
November	0	–	–
December	8	136	17.0
Total	34	537	15.8

[a] All cases are attributed to the month in which the index case occurred.

[b] Outbreak No. 22; one exceptionally large outbreak occurred at the end of the epidemic season.

Case Studies of Importations into Europe

Detailed accounts of 2 outbreaks following importations into Europe are given elsewhere: outbreak No. 31 in Chapter 4, as an example of the airborne transmission of smallpox, and outbreak No. 33 later in this chapter, as part of the epidemic that spread across south-western Asia into Europe in 1970–1972.

Two other examples illustrate different aspects of smallpox outbreaks after importations into Europe: an outbreak (No. 16) in Bradford, England, in 1961, in which

BY COURTESY OF MESCHEDE HOSPITAL

Plate 23.3. The airborne spread of virus from this 20-year-old electrician, infected in Pakistan, caused smallpox in 17 other patients in the 1970 outbreak in Meschede Hospital, Federal Republic of Germany, described in Chapter 4. He had had no direct contact with any of them.

transmission occurred in 3 hospitals; and an episode (No. 32) in Denmark and Norway in 1970 that led to only 1 further case despite the original patient's having had numerous contacts.

The Bradford outbreak

The outbreak in Bradford started with a 9-year-old Pakistani girl, who developed smallpox in December 1961. She had travelled with her family from Karachi to London by air on 16 December 1961, and then by train to Bradford on 17 December (England and Wales, Ministry of Health, 1963). On 5 December, she had been vaccinated against smallpox and issued with an international certificate of vaccination. On 23 December she was admitted to Bradford Children's Hospital with symptoms of malaria, and the presence of *Plasmodium vivax* was confirmed by blood examination. She responded to antimalarial drugs and was afebrile from 24 to 26 December. On 27 December she developed a low-grade fever and became apathetic and listless. Two days later her temperature rose to 40 °C. On 30 December she developed petechiae on her face and neck and died. A post-mortem examination on 1 January 1962 attributed death to staphylococcal septicaemia and malaria. She was flown to Pakistan to be buried. Smallpox was not suspected; even the physical evidence of recent vaccination was not noted.

Between 11 and 13 January 1962, 10 first-generation cases of smallpox were discovered in the Bradford area (Fig. 23.2) and virologically confirmed. All were unvaccinated before this episode, except case No. 2, in a 40-year-old visitor to an affected ward at Bradford Children's Hospital—a man who had been vaccinated while a member of the armed services during the Second World War—and case No. 3, a resident cook at the Bradford Children's Hospital, who became ill on 6 January. The cook was admitted on 11 January to the Leeds Road Hospital, where a diagnosis of smallpox was made; she died the next day. The other cases were in 6 unvaccinated child inpatients (cases No. 4–No. 9), an 18-year old nurse (case No. 10), and the 37-year-old pathologist (case No. 11) who had performed the post-mortem on the index case; 5 died.

The patients were promptly isolated and vaccinated; only 3 second-generation cases were recognized. The first 2 of these were in elderly male patients (cases No. 12 and No. 13) in the ward of another hospital (St Luke's) to which case No. 2 had been admitted just prior to his death. The third was a boy (case No. 14) who had been in contact with case No. 6, a child who had been transferred to the Wharfedale Children's Hospital. All 3 second-generation cases were confirmed virologically; 2 recovered and 1 died, apparently from a heart attack.

To sum up, the Bradford outbreak comprised 14 cases; 7 of the patients died, 6 of them from smallpox. All the indigenous infections were contracted in hospital, and 4 hospitals were involved, with transmission in 3 of them. The outbreak was already rather large by the time it was recognized as being caused by smallpox, and there had been numerous opportunities for transmission, both within hospitals and in the general community. The task of identifying, tracing and vaccinating more than 1400 contacts and keeping them under surveillance was expensive, difficult and time-consuming. Although mass vaccination was never contemplated, vaccination clinics were opened because so many people had been already exposed by the time the outbreak was recognized. Practically the whole of the town's population of 250 000 was vaccinated within 5 days (Douglas & Edgar, 1962).

This episode illustrates the unpreparedness of hospitals in the United Kingdom to cope with an outbreak of smallpox at that time, given the large proportion of unvaccinated professional and domestic staff, the difficulty of recognizing haemorrhagic-type smallpox and the risks thereby incurred, and the problems encountered in effectively containing the outbreak once it had been recognized. The response to the provision of vaccination clinics demonstrated the existence of considerable public fear and apprehension about smallpox.

Outbreak in Skodsborg, Denmark, and Tromsö, Norway

In August 1970 smallpox was imported into Denmark by a 22-year-old Danish medical student who had returned to Copenhagen after a curtailed holiday in Afghanistan. He had been successfully vaccinated in 1956 in Norway and revaccinated with liquid vaccine in May 1970, but the result had not been checked and he said later that the revaccination had been unsuccessful. He arrived in

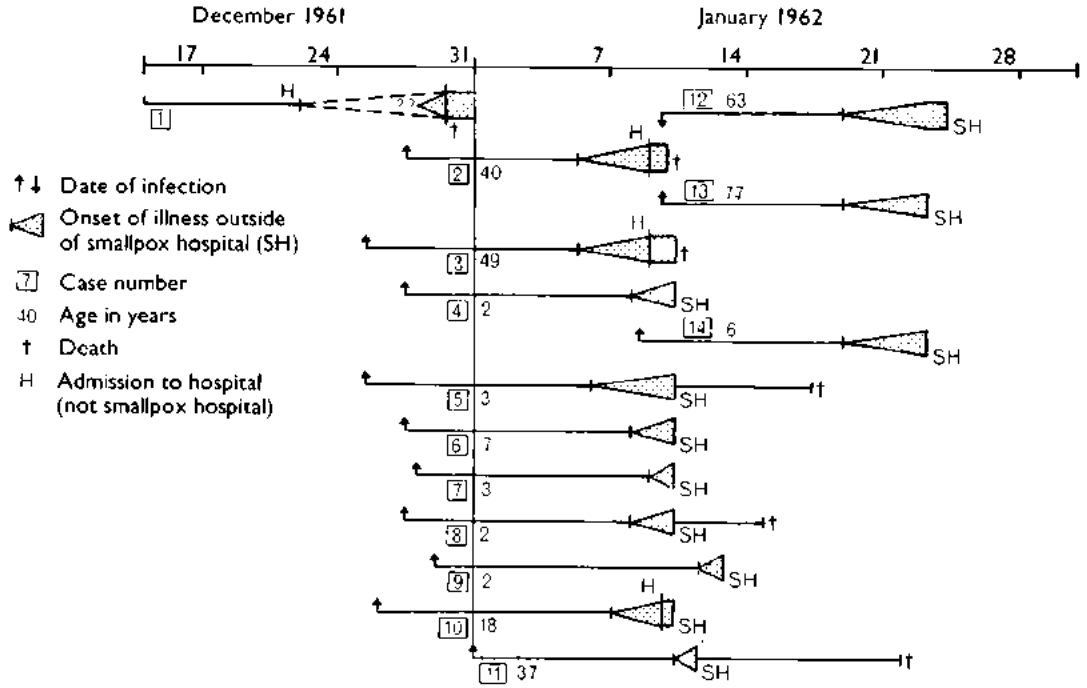


Fig. 23.2. Outbreak of smallpox in Bradford, England, in December 1961 – January 1962. All cases were hospital-associated. The index case was a Pakistani girl who was admitted to the Bradford Children's Hospital and died of unrecognized haemorrhagic smallpox. Cases No. 4-9 were patients at that hospital, case No. 2 a hospital visitor, and cases No. 3,10, and 11 a resident cook, a nurse and the pathologist, respectively. The three second-generation cases occurred at another hospital to which case No. 2 had been admitted, and case No. 14 at a third hospital to which case No. 4 had been admitted before it was realized that he had smallpox. (Based on England and Wales, Ministry of Health, 1963.)

Kabul early in August, and was admitted to hospital on the 14th, suffering from severe gastroenteritis. Because cholera was suspected, he was transferred to the infectious diseases ward, where he was exposed to cases of smallpox between 17 and 19 August. On 26 August he returned to Copenhagen, feeling reasonably well and with a normal temperature.

On 28 August, when he was living in the staff quarters of the Skodsborg Hospital, near Copenhagen, he became feverish and was treated with penicillin. The next day he developed a rash, which was attributed to the penicillin. On 31 August he was admitted to the infectious diseases ward of the Blegdam Hospital with a diagnosis of pneumonia and dysentery. On 2 September, smallpox was suspected and he was placed in isolation. The State Serum Institute in Copenhagen confirmed the diagnosis by laboratory examination a day later. On 4 September the rash became confluent and haemorrhagic, and secondary infection occurred, with severe pneumonia. He later developed renal symptoms and died.

Some 400 direct or indirect contacts of the patient were identified, traced, vaccinated and put into quarantine at the Blegdam Hospital. They were mainly persons who had lived with the medical student in the dormitory at the Skodsborg Hospital and personnel at the Blegdam Hospital who had cared for the patient or had had contact with his clothing and bed-linen.

The Danish health authorities at no time contemplated mass vaccination, but maintained an alert for potential secondary cases until mid-October, because there might have been a missed case which would be detected only if the infection were transmitted to others. However, the only subsequent case that did occur was recognized in Norway.

Smallpox infection was carried to Tromsö, in the far north of Norway, by a 25-year-old Norwegian medical student who had been living in the staff quarters of the Skodsborg Hospital in a room next to that of the Danish

student. On 28 August, after they had talked briefly, the Norwegian student had left for Norway, travelling by car with another young Norwegian.

At the beginning of September, when the case in Denmark was confirmed as smallpox, the Norwegian medical student was identified by the Danish national health service as being a close contact. The Norwegian health authorities were notified, and on 4 September he was traced, vaccinated and kept under surveillance. Five days after vaccination he developed an accelerated reaction on the vaccination site. On 5 September, 9 days after contact, he developed low back pain and a rash suggestive of smallpox. Paired sera were sent to Oslo for serological tests, the results of which indicated smallpox. The person who had driven with him from Skodsborg to Norway and 33 other possible contacts were traced, vaccinated and isolated, but no further case occurred. This pattern, with good surveillance and minimal or no secondary spread, occurred in about half of the recognized importations into Europe during the period 1959–1973.

IMPORTATIONS INTO NORTH AMERICA AFTER 1959

The transmission of smallpox had been interrupted in the USA and its territories in 1949. In that year the last known outbreak, resulting in 8 cases and 1 death, occurred in Texas and was probably due to an importation from Mexico, in which the last case of smallpox occurred in 1951. Reports of smallpox during the 1950s turned out on further investigation to have been cases of chickenpox. In Canada, endemic smallpox was eliminated in 1943, but there were 7 imported cases in 1945 and 1946.

As international air traffic increased in the 1960s and 1970s, and many more people travelled from Canada and the USA to Africa, South America and Asia, in which smallpox was still endemic, there was a constant and increasing risk of importing smallpox into North America. In contrast to Europe, there were no introductions of variola major from the Indian subcontinent into North America, despite the fact that Americans were the most numerous short-term travellers to the subcontinent. For example, Mack (1972) estimated that there were over 3 times as many travellers to India from the USA as from the Federal Republic of Germany (in 1969, 50 000 Americans compared with 14 000 Germans). However, after 1958, there were 5 importations from India into the Federal Republic of Germany but none into the USA. Only 1 importation of smallpox into North America was reported—a single case of variola minor imported from Brazil into Canada via the USA.

Sixteen years after Canada's last case of smallpox, the disease was brought back to Toronto from Brazil in 1962 by a 15-year-old Canadian boy, who had lived for several years in Paraná State, Brazil. At the end of July 1962 he had been in contact with 4 children who were said to be suffering from chickenpox. On 10 August he and his family left Brazil by air and arrived in New York City on 11 August. Just before his departure from Brazil, the boy had developed fever and malaise which were diagnosed as influenza. On arrival in New York he had presented a smallpox vaccination certificate dated 22 July 1962 (*Wkly epidem. rec.*, 1962), but in fact he had not been vaccinated for approximately 6 years (Best & Davis, 1965).

The family remained in New York for some 6 hours before boarding a train to Toronto. Soon after his arrival there on 12 August, the boy developed a rash, which 2 days later had spread widely over the body, showing a typical centrifugal distribution. He was admitted to hospital in Toronto on 18 August. The clinical diagnosis of smallpox was confirmed on 20 August by the isolation of variola virus. Passengers on the plane on which he had travelled from Brazil to New York were identified, vaccinated and placed under surveillance, as were the members of his family and other known close contacts in Toronto. Persons who had travelled on the train from New York or had had possible contact in the railway stations were requested through the mass media to report for vaccination, and those who did so were also placed under surveillance. No additional cases were reported.

IMPORTATIONS INTO JAPAN

Japan, the only large industrialized country in eastern Asia, had been free of smallpox since 1951. There were a few imported cases each year until 1955; then, after an absence of smallpox for 18 years, 2 importations oc-

Plate 23.4. The Japanese government official who was infected in Dhaka in 1973 worked in this conference room of the parliament building in Tokyo while suffering the prodromal symptoms of smallpox, which was diagnosed a few days later. Health officials disinfected the room.

curred, in 1973 and 1974, at a time when the number of travellers from Japan to the Indian subcontinent had increased substantially. The first case was in a 33-year-old Japanese traveller, who had stayed in Dhaka, Bangladesh, from February to mid-March 1973, when Dhaka and its surrounding areas were experiencing an extensive epidemic of smallpox (see Chapter 16). The patient, who was reported to have been vaccinated in mid-January, returned to Tokyo via Bangkok on 18 March, became ill on 23 March and was hospitalized on 26 March. On 31 March he was isolated in the Tokyo Metropolitan Infectious Diseases Hospital and a diagnosis of smallpox was virologically confirmed a day later. Close contacts were identified and placed under surveillance, but no secondary cases occurred (*Wkly epidem. rec.*, 1973a).

The second importation into Japan occurred in January 1974 (*Wkly epidem. rec.*, 1974). The index case was a Japanese Buddhist pilgrim, who was exposed to smallpox while travelling through northern India. He had no record of vaccination in childhood, and the result of his vaccination in Japan on 7 December 1973 was interpreted to be a "reaction of immunity". He developed symptoms on 22 January 1974, 5 days after his return to Japan. Control measures, initiated on 28 January, when smallpox was suspected, included the isolation of the patient and his family, and the vaccination and surveillance of some 270 persons considered to be close contacts, including 19 pilgrims who had accompanied the patient to India. No secondary cases occurred.

IMPORTATIONS INTO RECENTLY ENDEMIC COUNTRIES, 1959–1976

Besides the countries of Europe, North and Central America, Oceania and eastern Asia in which smallpox was not endemic in 1959 (see Chapter 9, Fig. 9.3), there were a number of countries in Africa, South America, south-eastern Asia and south-western Asia in which smallpox had been endemic in the 1950s but had been eliminated during the next decade, and which were thereafter exposed to the risk of importations from neighbouring endemic areas. Importations also occurred across the borders of countries that continued to

Table 23.6 Africa: last year of smallpox endemicity in individual countries or territories

Number of countries	Year	Country or territory
13	1958 or before	Central African Republic,[a] Congo,[a] Egypt, Gabon,[a] Guinea-Bissau, Lesotho,[a] Libya, Madagascar, Morocco, Namibia, South Africa,[a] Swaziland,[a] Tunisia
17	1959	Angola, Djibouti
	1960	Equatorial Guinea
	1961	Algeria
	1962	*Lesotho*, Mauritania, Somalia,[a] Sudan[a]
	1963	*Central African Republic*, Senegal
	1964	Botswana[a]
	1965	Chad, *Congo*, *Gabon*
	1966	Côte d'Ivoire, Gambia, *Swaziland*
26	1967	Ghana
	1968	Cameroon, Guinea, Liberia, Mali, Niger, Uganda, Upper Volta (Burkina Faso), Zambia
	1969	Dahomey (Benin), Kenya, Mozambique, Sierra Leone, Togo
	1970	Burundi, Nigeria, Rwanda, Southern Rhodesia (Zimbabwe), United Republic of Tanzania
	1971	Malawi, *South Africa*, Zaire
	1972	*Sudan*
	1973	*Botswana*
	1976	Ethiopia
	1977	*Somalia*

[a] Endemic smallpox re-established later, and subsequently eliminated, in the year indicated by the italicizing of the country's name.

harbour foci of endemic smallpox (see, for example, Chapter 15, which discusses importations from India into Nepal).

Data on importations into non-endemic countries of South America are reasonably complete from 1959 onwards, but data from Africa and Asia were very scanty prior to the establishment of the Intensified Smallpox Eradication Programme in 1967. Even after 1967, not much information is available on importations into African countries. Comments on importations into these continents are therefore limited to tabulations of importations from one country into another within each continent, from 1959 for South America, and from 1967 for Africa and Asia. However, a connected series of outbreaks in Iran, Iraq and the Syrian Arab Republic in 1970–1972 will be described in greater detail.

Africa

By 1958, 13 of the 47 countries of Africa appeared to have become free of endemic smallpox. In the period 1959–1966, when WHO encouraged the remaining African States to institute national smallpox eradication programmes, 17 countries (5 of them reinfected) are believed to have succeeded in interrupting smallpox transmission (Table 23.6). When the WHO Intensified Smallpox Eradication Programme began in Africa in 1967, smallpox was endemic in 23 countries, and between 1968 and 1976 endemicity was re-established in 3 countries.

Between 1967 and 1976, over 70 importations of smallpox from neighbouring endemic countries into non-endemic countries were reported (Table 23.7). International boundaries in Africa, most of them drawn during the 19th century by the European colonial powers, bore little relationship to ethnic or tribal distribution, so that many of them were crossed and recrossed as frequently as were state or district boundaries in a country such as India. The transfer of smallpox across these boundaries occurred repeatedly, and the figures for importations in the late 1960s, when smallpox was becoming much less common and surveillance was improving, are not complete. It is known that in several instances (indicated by the symbol "+" in Table 23.7) there were more importations than those reported; it is also clear that importations from Ethiopia into neighbouring countries were at least as numerous before 1971 as after that year, when effective surveillance began.

In most cases the disease did not persist long after importation, as, for example, after the numerous transfers from Ethiopia to Djibouti and Somalia between 1971 and 1975. However, importations into the Sudan (1967), Botswana (1971) and Somalia (1976) led to the re-establishment of endemicity in the recipient countries and had a considerable impact on the global eradication programme. In each country, transmission persisted until a full-scale eradication programme had been set up and the local health staff had grasped the concept of surveillance and containment, which enabled them finally to interrupt transmission. Of more than 17 importations into non-endemic countries of western Africa that were recorded after 1966, at least 10 originated in Nigeria. Ethiopia was an even more important source country: all but 7 out of more than 47 importations reported anywhere in Africa between 1971 and 1976 originated there.

Table 23.7 Africa: non-endemic countries experiencing importations, 1967–1976, by region

Country of origin			Importing country and year of importation[a]									
Name	Last endemic	Number of incidents	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976
Western Africa												
Niger	1968	1	–	–	Mali							
Nigeria	1970	10+	Chad (4+) Sudan Ghana	Chad (1+)	Cameroon (1+) Niger							
Togo	1969	6	–	Ghana (6)	–							
Southern Africa												
Botswana	1973	1	–	–	–	–	–	South Africa				
South Africa	1971	1+	–	–	–	–	Botswana (1+)[b]					
Southern Rhodesia (Zimbabwe)	1970	1	Botswana	–	–	–						
Central Africa and the Horn of Africa												
Ethiopia	1976	41+	Sudan (1+)[c]	–	–	–	Djibouti (2) Kenya (2)	Djibouti (3) Somalia (4)	Djibouti (9) Somalia (4) Kenya (1)	Djibouti (2) Somalia (6)	Somalia (2)	Somalia (4+)[d] Kenya (1)
Rwanda	1970	1	–	–	–	Uganda						
Zaire	1971	2	–	–	–	Uganda Zambia						
Sudan	1972	7+	–	–	Uganda (1+)	Uganda (1+)	Uganda (2+)	Uganda (3+)				

[a] Numbers in brackets indicate number of separate importations in the year indicated.
[b] This importation led to the re-establishment of endemic smallpox in Botswana (see Chapter 20).
[c] This importation led to the re-establishment of endemic smallpox in the Sudan (see Chapter 18).
[d] The last of these importations led to the re-establishment of endemic smallpox in Somalia (see Chapter 22).

Table 23.8 South America: reported importations of smallpox into non-endemic countries, 1959–1970[a]

Year	Countries receiving importations from:	
	Argentina (last endemic, 1966)	Brazil (last endemic, 1971)
1959	Chile (1)	–
1960	–	Uruguay (19)
1961	–	Uruguay (1)
1962	–	Venezuela (11)
1962	–	Uruguay (10)
1963	Chile (3)	Uruguay (1)
1963	–	Peru (endemic)
1964	–	Uruguay (3)
1964	–	Bolivia (5)
1964	–	Paraguay (7)
1965	–	Uruguay (1)
1965	–	Paraguay (30)
1966	–	–
1967	–	Argentina (30)
1968	–	French Guiana (1)
1968	–	Uruguay (2)
1969	–	Uruguay (1)
1969	–	Uruguay (1)
1969	–	Uruguay (1)
1970	–	Argentina (24)

[a] Numbers in brackets indicate the number of reported cases associated with each importation.

South America

By 1959 smallpox transmission had been interrupted in Chile, Peru, Uruguay and Venezuela. In the 8-year period from 1959 to 1966 another 5 countries became smallpox-free: Argentina, Bolivia, Colombia, Ecuador and Paraguay. Except in Peru, importations during the period 1959–1970 did not result in large numbers of cases. However, in Peru in 1963, following its introduction from Brazil, variola minor became endemic and remained so until 1966. From 1964 onwards, Brazil was the only known source from which smallpox was exported to other countries in the subcontinent (Table 23.8).

Southern Asia

Apart from importations into countries of south-eastern Asia that had long been smallpox-free (see Chapter 8), information on importations into the non-endemic non-industrialized countries in Asia is fragmentary before 1967 and still incomplete after that date. What is known can be most effectively discussed in respect of 2 regions: countries adjacent to India, and south-western Asia.

Countries adjacent to India

Reported importations into non-endemic countries near India during the period 1967–1974 are shown in Table 23.9. The 12 outbreaks fall into 5 groups: importations into Sri Lanka, Afghanistan, Bangladesh, Bhutan and Burma.

Importations into Sri Lanka (outbreaks No. 2 and No. 6) and Afghanistan (3 outbreaks, grouped together as No. 7) were effectively contained. Sri Lanka had been free of endemic smallpox since 1951 and was vigilant in its efforts to maintain that status. The 2 reported cases were contained without local spread, vaccination being carried out on a large scale in Kandy (outbreak No. 2) and Colombo (outbreak No. 6) respectively. Three importations into Afghanistan occurred in 1973, the year after smallpox had been eliminated; they were discovered promptly and the containment methods used during the eradication programme limited spread.

The importation of smallpox into Bangladesh early in 1972, following the return from India of millions of refugees, led to the re-establishment of endemic smallpox and to many thousands of cases. Eradication was not achieved until October 1975.

Table 23.9 Importations of smallpox into non-endemic countries adjacent to India, 1967–1974

Serial number	Year	Importing country	Country of origin	Number of reported cases	Comment
1	1967	Bhutan	India	14	2 outbreaks, originated in markets in Assam.
2	1967	Sri Lanka	India	1	–
3	1968	Burma	East Pakistan	181	Affected 14 villages, over a period of 7 months.
4	1969	Burma	East Pakistan	68	Affected 3 villages, over a period of 2 months.
5	1972	Bangladesh	India	Numerous	Refugees returning from India re-established endemicity in Bangladesh.
6	1972	Sri Lanka	Afghanistan	1	German tourist infected.
7	1973	Afghanistan	Pakistan	25	3 outbreaks of 1, 11, and 13 cases respectively.
8	1973	Bhutan	India	6	Originated in West Bengal.
9	1974	Bhutan	India	3	Originated in Assam.

From an epidemiological standpoint, Bhutan is equivalent to an Indian state, so that it is not surprising that smallpox spread across the border from Assam (outbreaks No. 1, No. 8, and No. 9). Because of the small and sparse population the disease did not persist. In Burma, on the other hand, introductions from Chittagong, East Pakistan (Bangladesh), in 1968 and 1969, shortly after smallpox had been eliminated (outbreaks No. 3 and No. 4), spread without control for several months, because it was very difficult for the health services to operate in the area, in which there were many insurgents.

South-western Asia

This region (Fig. 23.3) consists of Iran (now the Islamic Republic of Iran) and Iraq to the north, Israel, Jordan, Lebanon and the Syrian Arab Republic to the west, and the Arabian peninsula, comprising Democratic Yemen, Saudi Arabia, Yemen, and the 5 Gulf states of Bahrain, Kuwait, Oman, Qatar and the United Arab Emirates. The Arabian Peninsula is mostly desert and the majority of the population is concentrated in a few cities. However, this area was the crossroads of smallpox transmission, since between 1 and 2 million pilgrims came to Mecca by sea, land and air every year, many from the endemic countries of Africa and Asia. Even more important were the numerous migrant workers in the Gulf states, mostly from Pakistan and India.

By 1963, all countries in south-western Asia, except Yemen, appeared to have interrupted smallpox transmission, but frequent importations, particularly from the Indian subcontinent, and deficiencies in the notification of cases to WHO (including the occasional suppression of reports) made it very difficult to know precisely when these countries became non-endemic and to judge the magnitude of outbreaks following importations (Table 23.10). Smallpox was poorly reported, not only because of inadequate health services, but also because of national pride and the fear that the presence of the disease might lead to restrictions on travel or the imposition of an economic embargo by neighbouring countries. In Saudi Arabia, it was believed that reports of the presence of smallpox would inhibit visits by pilgrims. The reliance of some countries in this area on their own capacity to control outbreaks of smallpox occasionally resulted in large numbers of cases and the spread of the disease for up to 2 years. In some of these countries, moreover, clinical and laboratory diagnoses were unreliable, so that the health services could not be certain whether the cases that they recorded were indeed smallpox. They hesitated to request WHO's assistance in improving laboratory diagnosis, because the rendering of such support might lead to international disclosure of the suppression of information about outbreaks.

Between 1967 and 1972, Iran, Iraq, Kuwait, Saudi Arabia, the Syrian Arab Republic, or the United Arab Emirates continued to report cases of imported smallpox every year except 1969. Brief comments on these outbreaks are provided in Table 23.10. The

Table 23.10 Importations of smallpox into non-endemic countries of south-western Asia, 1967–1972

Serial number	Year	Importing country	Country of origin	Number of reported cases	Comment
1	1967	Kuwait	Bangladesh	41	Hospital-associated outbreak (Arita et al., 1970); probably spread to Iran.
2	1967	United Arab Emirates	India	10	Probably 3 importations from different dhows (Swinhoe, 1970).
3	1968	United Arab Emirates	India	1	No local spread.
4	1968	United Arab Emirates	India	1	
5	1970	Iran	Afghanistan	29 (1971) 2 (1972)	Reports suppressed; origin of large epidemic that spread westwards (No. 9 and No. 10), eventually reaching Europe.
6	1970	Saudi Arabia	Bangladesh	12	Pilgrims on ship which was quarantined in harbour.
7	1970	Saudi Arabia	?	2	Diagnosed by WHO epidemiologist in Riyadh area; not reported by national authorities.
8	1970	United Arab Emirates	Pakistan	48	Outbreak lasted until June 1971; greatly underreported.
9	1971	Iraq	Iran	37 (1972)	Extension of No. 5; disease became endemic.
10	1972	Syrian Arab Republic	Iraq	54	Extension of No. 9; hundreds of cases, but outbreak controlled within 4 months.

Suppression of Information on Quarantinable Diseases

Suppression of the reporting of diseases of international importance has been—and remains—a common practice in many countries, both developing and developed. So far as the countries of south-western Asia are concerned, the failure to report smallpox can be ascribed in part to recent experience with cholera. This disease, which had been absent from the area for many years, was reintroduced in the mid-1960s. Governments were unfamiliar with it, and although the outbreaks were caused by the milder *eltor* biotype, there were many deaths. A variety of measures were introduced to control the spread of cholera, including the imposition of a cordon sanitaire, prohibition of the import of goods and widespread vaccination. These had a serious economic impact, which led some governments to suppress reports of the disease. Against this background, it is not surprising that when smallpox was reintroduced after an absence of many years, governments sometimes responded by not reporting. Suppression of information occurred not only at the central national level, but also often at lower peripheral levels within countries. Smallpox, however, was rather more difficult to conceal than cholera.

WHO actively sought to discourage the suppression of reports of smallpox. Several approaches were used. Endemic countries were encouraged to report fully, and when this led to an apparent increase in the recorded incidence the governments were congratulated on their improved surveillance. As the numbers of smallpox cases declined, WHO encouraged countries to offer a reward for reporting cases to both health personnel and the public, to make it clear that government officials appreciated receiving this information. Finally, when rumours of smallpox in what was thought to be a smallpox-free country were reported by such persons as visitors or foreign officials, governments were asked to institute inquiries.

1970–1972 outbreak, which originated in Afghanistan and spread through 4 countries—Iran, Iraq, the Syrian Arab Republic and Yugoslavia—was of particular interest and importance, because of its extent, the degree of underreporting, and its occurrence at a time when the Intensified Smallpox Eradication Programme was in full swing.

THE 1970–1972 OUTBREAK IN SOUTH-WESTERN ASIA AND EUROPE

Iran officially reported 29 cases in 1971 and 2 in 1972; Iraq reported 37 cases and the Syrian Arab Republic 54 cases in 1972 (Table 23.10). However, it was known that the actual numbers of cases were much greater, especially in Iran, and it was feared that the epidemic in these countries would cause a substantial set-back to the global eradication programme.

Epidemic spread began in Iran towards the end of 1970, but reports of cases were suppressed. Iran had eliminated smallpox in 1963 by a well-organized mass vaccination campaign; one additional outbreak is known to have occurred in Khorramshahr in 1967, but it was not reported. Apart from this experience and the excessive measures recently taken against countries which had reported cholera, the authorities in Iran had also to take into account the forthcoming major celebrations commemorating the 2500th anniversary of the Persian Empire, which they did not wish to jeopardize; the major function was to be held in Persepolis, in Fars Province, on 12 October 1971, and the heads of state and dignitaries from more than 100 countries were to attend it.

However, extensive outbreaks of smallpox could not long go undetected in a large, cosmopolitan country such as Iran. Acting on information received through the United States Center for Disease Control, WHO sent a cable to Iran on 13 January 1971: "Informed presence smallpox cases 46, deaths 8, Tabriz, E. Azerbaijan province ... appreciate any additional information." About a month later Iran cabled that 9 cases had, indeed, occurred, saying that 3 infected Afghans in Mashhad had led to 4 more cases there and 2 in Tabriz.

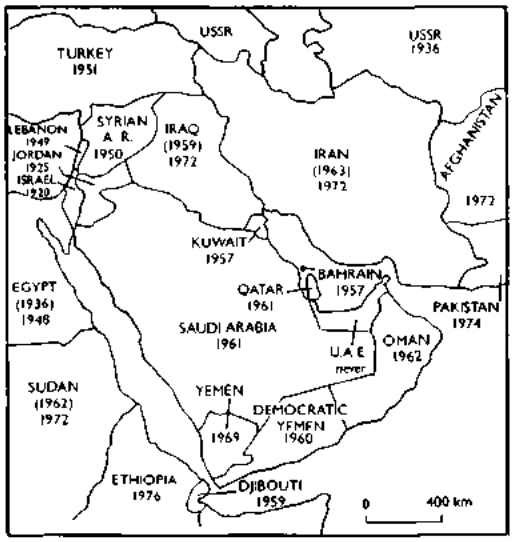


Fig. 23.3. South-western Asia: years in which smallpox ceased to be endemic in each country, before the 1970–1972 epidemic in Iran, Iraq and the Syrian Arab Republic.

No epidemiological details were given and no further cases were reported.

During the following months, reports of smallpox in Iran from various sources grew more and more numerous until finally, on 17 November 1971, the Surgeon General of the United States Public Health Service cabled the following message to the Director-General of WHO: "Reliable reports of smallpox in Shiraz and Abadan, Iran. Can you inquire as to the validity of the report? Until matter resolved U.S. will require valid [vaccination] certificates of arrivals from Iran." It should be noted that the USA had discontinued routine vaccination in 1971 and naturally a smallpox epidemic in a country with which the USA was in close contact was of great concern. Iran's cabled response to an inquiry from WHO, 11 days later, was that 20 cases had occurred between 28 August and 3 October 1971 but none since then, making a total of 29 acknowledged and reported cases in 1971.

Nothing further was heard until 6 March 1972, when Iran, without prompting, notified WHO that 2 cases had occurred on 16 January on its "eastern border". Following a request by WHO for more information, the Ministry of Health stated that the reported cases had occurred in the children of a Baluchi mother who normally lived in Quetta, Pakistan. No information was given as to their recent whereabouts in Pakistan, and at that time active surveillance had revealed no cases in the Quetta area.

At this point it became clear that an epidemic, which could no longer be concealed, was occurring—and not merely in Iran. On 5 March 1972, Iraq reported to WHO by cable that sporadic cases had occurred on its border with Iran and requested 500 000 doses of vaccine. On 17 March, Yugoslavia reported the presence of smallpox to WHO; on 25 March, the Syrian Arab Republic reported the discovery of 15 cases; and on 28 March, the Federal Republic of Germany notified a case in Hanover, in a man who had come from Yugoslavia. In the face of this evidence, the resistance of all the countries of south-western Asia to reporting the disease weakened, but it did not collapse.

Iran

Iran (population in 1972, 30.3 million) officially reported 31 cases of smallpox in 1971–1972. The suspicion that there had been many more cases was confirmed following a visit to Iran by Henderson from 2 to 13 August 1972. He reported that over 2000 cases had been hospitalized and that 6000–8000 cases had probably occurred. Subsequently, a confidential government report supplied to the Global Commission for the

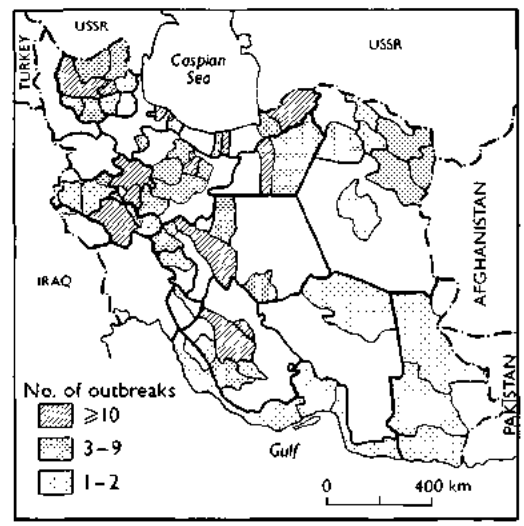


Fig. 23.4. Iran: distribution by district of 400 smallpox outbreaks with some 2000 locally reported cases over the period between November 1970 and September 1972.

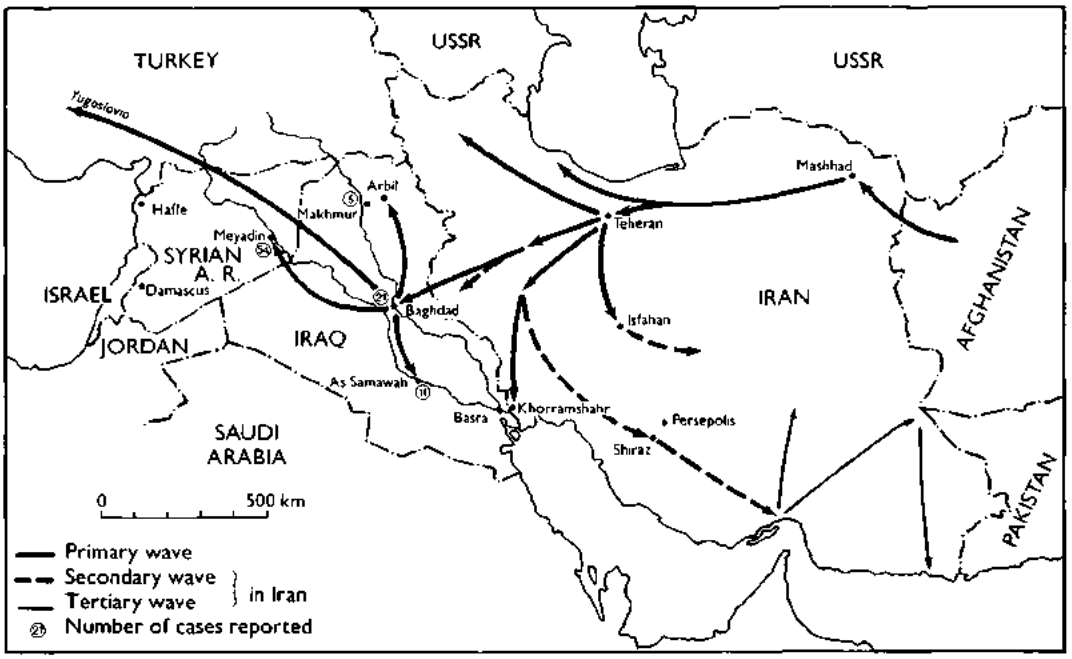


Fig. 23.5. Spread of smallpox in Iran, Iraq and the Syrian Arab Republic, 1970–1972. The disease was introduced from Afghanistan into Mashhad, Iran, in October 1970. There were three waves of dispersion through Iran, which lasted over a period of 22 months. By the end of 1971 smallpox had crossed into Iraq, where it spread north to Arbil and south to As Samawah. Transmission in Iraq was interrupted by June 1972. In February 1972, smallpox spread from Baghdad in Iraq to Meyadin in the Syrian Arab Republic, where a smaller outbreak occurred that was contained by June 1972.

Certification of Smallpox Eradication in December 1978 gave details of 1996 cases in 400 widespread outbreaks between November 1970 and September 1972 (Fig. 23.4). Of these cases, 1349 had been confirmed by laboratory tests.

The epidemic seems to have started when an Afghan family of 6 left their village near Kabul on 16 October 1970 and began a pilgrimage through the smallpox-endemic areas of Afghanistan to the holy city of Mashhad, in Khorasan Province in north-eastern Iran, where several thousand pilgrims congregate daily during the hadj. The family arrived in Mashhad on 20 October. One of the children developed a rash on 3 November and 2 others were similarly afflicted 6 weeks later. Although the first imported case was apparently promptly diagnosed by a local health worker, the disease had already been transmitted to many other pilgrims.

The primary wave of smallpox spread to another 6 provinces in the north (Fig. 23.5), which were to be the most severely affected and for the longest time. Once smallpox reached Teheran it was amplified by hospital-associated spread, and became a typical urban outbreak affecting slum areas and semi-urban districts around the city. Teheran and the original foci in the northern provinces became the principal sources of infection for another 12 provinces in the west-central part of the country during 1971, from which 2 more in the southern part were affected in 1972. Subsequent review suggested that the confidential report, which had noted that 73% of the cases occurred in cities, seriously underreported the numbers of cases occurring in the rural areas.

The strategy adopted by the health authorities was containment by mass vaccination, with only a rudimentary surveillance component. The little freeze-dried vaccine available was below standard; liquid vaccine was used for most vaccinations. Primary take rates were reported to be no more than 65%. Many persons who claimed to have been vaccinated subsequently developed the disease. Although it was reported that 12.5 million vaccinations had been performed in 1970 and 19.8 million in 1971, smallpox continued to spread throughout Iran. There were major outbreaks

in Shiraz, which was the largest city near Persepolis, where the celebrations were to be staged. The health authorities conducted repeated mass vaccination campaigns in Shiraz itself, but partly because liquid vaccine of low potency was being used, transmission was not interrupted. The authorities were in a quandary; they recognized that the vaccine was of low potency, but could not apply to WHO for potent vaccine because of instructions issued at a higher level of government. Eventually, in November 1971, freeze-dried vaccine was sent to Iran by WHO Headquarters: 2 million doses in 1971, followed by 11 million in 1972. A second round of mass vaccination was performed and during 1972 more than 20.6 million people were vaccinated. The last case of smallpox in Iran was reported from Fars Province, with onset of rash in September 1972.

The epidemic in Iran lasted for 22 months, and at least 400 outbreaks occurred in 70 out of the 162 districts in the country.

Iraq

Once the Iranian outbreak had begun in Mashhad in November 1970, smallpox moved relatively quickly along the main road to Teheran and Kermanshah, which is the principal route to Baghdad, the capital of Iraq (population in 1972, 10 million). It seems likely that smallpox arrived in Baghdad at the end of 1971 and then spread north and south along the principal roads running parallel to the Tigris and Euphrates rivers (see Fig. 23.5). An estimated 800 cases of smallpox probably occurred in the country, the last case being in Baghdad in June 1972.

The presence of smallpox in Iraq first came to the attention of WHO when a cable was received on 5 March 1972 reporting the presence of smallpox cases on its northern border with Iran and requesting 500 000 doses of vaccine. The Smallpox Eradication unit received further information on the outbreak on 8 March, during the debriefing of Dr N. Maltseva, who had been touring vaccine production facilities in Iraq, Iran and the Syrian Arab Republic in January and February. She reported that there had been cases of smallpox in Baghdad in January. On 18 March, Iraq informed WHO that 20 cases had occurred in widely separated areas: in Arbil in the north-east, in Baghdad, and in As Samawah in the south. A letter dated 19 March from the Ministry of Health mentioned 2 more cases and stated that the infection had spread from Arbil to Baghdad and from there to As Samawah. It was reported that all known cases had been isolated in fever hospitals and that contacts had been vaccinated and placed under strict surveillance. The population of areas in which cases had been notified were subjected to mass vaccination and surveillance measures were instituted. All provinces had been requested to intensify the mass vaccination campaign begun in December 1971. Subsequently, it was reported that over 2.3 million vaccinations were performed in 1971, followed by 8.2 million in 1972 and 1.2 million in 1973.

Three more cases were reported in Baghdad in June and 1 in July 1972. In August Dr Ehsan Shafa, of the Smallpox Eradication unit, visited Iraq. He was presented with records of only 37 cases, with 5 deaths, in 3 provinces, for none of which could the source of infection be determined. However, the pilgrim responsible for the outbreak in Yugoslavia (see below) had been infected between 3 and 6 February 1972, before the onset of any of the reported cases. In addition to Dr Maltseva's report, an oral statement by a WHO nurse indicated that cases had occurred in a province for which data had not been provided. Furthermore, cases from Iraq had given rise to outbreaks in both Yugoslavia and the Syrian Arab Republic, and long experience with smallpox had shown that such exports to other countries usually indicated the presence of an outbreak of considerable size in the exporting country.

When Dr Shafa reviewed the data with a special technical committee in Iraq, the meeting agreed that a number of cases had been "overlooked" or "misdiagnosed". A more realistic estimate put the total number of cases at a minimum of 800. Nevertheless, the measures taken by the health authorities were found to have interrupted transmission in June 1972. Slow transmission might still have been going on undetected only to flare up later, but continued surveillance in the latter part of 1972 and in 1973 indicated that transmission did not continue after June 1972.

Syrian Arab Republic

On 25 March 1972, the Syrian health authorities notified WHO that cases of smallpox had been discovered in the Syrian

Arab Republic (population in 1972, 6.7 million). The index case was reported to be a 9-year-old boy who had visited Baghdad with his mother for a religious festival between 28 February and 5 March. He developed fever on 9 March, 4 days after his return from Iraq, and rash on 15 March. He was a pupil at the primary school in a village near Meyadin District (see Fig. 23.5). His condition was diagnosed at a dispensary as chickenpox, but on 21 March another schoolchild from the same locality, with a severe skin rash, was diagnosed by a physician in Meyadin as having smallpox. Simultaneously, a physician in another town diagnosed smallpox in 2 other schoolchildren with skin rashes. The disease spread through school contacts to the other villages in the area. A total of 54 cases and 2 deaths were reported, the date of onset of illness in the last case being 27 April 1972.

To control the outbreak, an isolation camp was established in Meyadin and the affected villages were cordoned off. Vaccination of everyone in the Syrian Arab Republic was made compulsory, starting with the affected region. WHO provided more than a million doses of freeze-dried vaccine and a supply of bifurcated needles in March 1972. Health centres and dispensaries were reported to have performed 75 748 vaccinations in 1971, 897 828 in 1972, and 106 176 in 1973.

There were inconsistencies in the data reported. The onset of illness in the index case occurred only a few days before the onset in those reported as secondary cases, an event which suggests multiple introductions or an earlier start to the outbreak. Nevertheless, the government had acted promptly in reporting to WHO and appeared to have done reasonably well in containing further spread.

However, pockmark surveys conducted in 1978 during the preparation of a report for the Global Commission for the Certification of Smallpox Eradication confirmed that far more cases had occurred in the Meyadin area in 1972 than had been reported (see Chapter 26). In fact, one case with pockmarks dating back to 1971 was found in Haffe District, on the other side of the country. Evidence of facial scarring, indicating the occurrence of cases in 1966–1967, which had not been reported, was also found. It was not clear in this instance whether the reporting of cases had been suppressed or whether cases had gone unnotified or had been misdiagnosed as chickenpox. However, the International Commission that visited the country in 1978 found that no smallpox had occurred there after 1972.

Yugoslavia

The reappearance of smallpox in Yugoslavia in 1972 (population in that year, 20.8 million), after more than 45 years without a case, was totally unexpected and caused great concern throughout the world. The epidemic has been described by Stojkovic et al. (1974) and, more briefly, by Litvinjenko et al. (WHO/SE/73.57).

Origin of the epidemic

The outbreak began with an infected pilgrim returning from Iraq. A bus-load of 25 Muslims from the semi-autonomous province of Kosovo in the south of Yugoslavia left on a pilgrimage to Mecca and Medina on 1 January 1972. On their way home they spent 3 nights in Baghdad and visited religious sites between Basra and Baghdad from 3 to 6 February, before leaving for Yugoslavia. The index case, a 38-year old Muslim priest, returned to his village of Danjane (population, 750), 20 kilometres north-east of Djakovica (Fig. 23.6), on 15 February 1972. The next day he fell ill with symptoms of fatigue, shivering and fever, which he thought were due to the

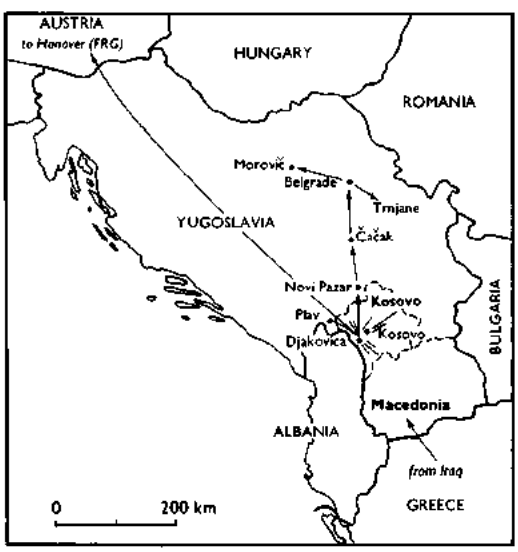


Fig. 23.6. Spread of smallpox in Yugoslavia in 1972. The index case arrived from Iraq on 15 February; the last 2 cases in Yugoslavia became ill in Kosovo and Belgrade on 11 April. The case in Hanover, Federal Republic of Germany, occurred on 22 March.

strenuous bus journey of several thousand kilometres. He denied ever having had a rash and a month later no evidence of skin lesions could be seen on his face or body. Although he had been vaccinated on 5 December 1971, no vaccination scar had developed. No one else on the bus contracted smallpox.

Spread of smallpox in Kosovo Province

A few days after his return, the index case was visited by many of his close relatives, friends and acquaintances, 11 of whom contracted smallpox. Nine cases occurred in Kosovo Province, 1 in Novi Pazar, 160 kilometres to the north (in Serbia), and 1 in a village north of Novi Pazar. These 11 cases were first generation cases, with onsets between 1 and 7 March (Fig. 23.7). None of them was suspected to be smallpox.

It was not until the evening of 14 March that smallpox was recognized by a doctor in the infectious diseases ward of the hospital in Prizren, in the district adjacent to Djakovica, who notified the federal health authorities of suspected smallpox in 4 patients coming from Danjane. The same day 4 other patients admitted to the hospital in Djakovica were recognized as having smallpox.

On 17 March the Yugoslav federal health authorities cabled to WHO that 8 cases of suspected smallpox had been detected. The clinical diagnosis was confirmed by laboratory tests on lesion material at the Institute of Immunology and Virology in Belgrade, confirmation being sent to WHO on 20 March. On 21 March, the WHO Regional Office for Europe informed Member States of the situation and a day later Dr R. Lindner, an Austrian epidemiologist who had previously worked in the Indonesian smallpox eradication programme, was sent to Yugoslavia as a WHO consultant to assist with the investigations.

Between 15 and 31 March, 100 additional cases of smallpox occurred among the immediate family members and relatives of known cases and among the patients of hospitals in Djakovica and Prizren, who had come into contact with cases before the correct diagnosis had been made (Fig. 23.7). This group formed the second generation of cases in Kosovo. Between 1 and 11 April, 14 more cases were recorded in Kosovo. With this third generation of cases the epidemic in Kosovo itself came to an end. It had affected 124 persons, of whom 26 died.

Spread of the disease outside Kosovo

A tragic and unusual chain of events led to considerable spread outside Kosovo. It started when a 30-year old teacher (Lj. M.), from a village near Novi Pazar, went to Djakovica on 21 February to enrol at the Higher Institute of Education. He came into contact with the index case, became feverish on 3 March after his return and developed a rash on 5 March, when he went to the local medical centre at Novi Pazar and was treated with penicillin. On 7 March he went by bus with his brother to the hospital in Čačak. After spending 8 March in the Dermatology and Venereal Diseases ward in Čačak, he was transferred by ambulance to the Belgrade Dermatology and Venereal Diseases Department on 9 March, because his condition was deteriorating. There he was shown to students and staff as a case demonstrating an unusual drug reaction to penicillin. With the development of severe haemorrhagic complications, the patient was taken, on 10 March, to the Surgical Clinic, where he died during the night. No one in any of the 4 medical establishments through which he had passed had had any suspicion that he might be suffering from smallpox. The brother of the deceased accompanied the body back to Novi Pazar, where it was buried on 12 March. The brother developed a rash on 20 March, and since the Yugoslav medical personnel were by then alerted to the disease, smallpox was diagnosed on 21 March. Only at this point was it realized that Lj. M. had died from haemorrhagic-type smallpox.

Retrospective epidemiological investigation showed that the patient had infected a total of 38 persons, 8 of whom died; 2 were infected in Novi Pazar, 9 in the Čačak hospital (8 patients and a nurse), and 27 in the Belgrade hospitals (20 patients and 7 hospital staff, including 2 physicians and a nurse). In view of the time that had elapsed before the diagnosis was made and of the difficulty of tracing the thousands of contacts of the patient, it was decided to undertake mass vaccination throughout Serbia. A few other cases occurred in additional foci outside Kosovo Province, and 1 case in a Yugoslav migrant worker, who became ill in Hanover, Federal Republic of Germany.

Control measures

On 15 March, a team of epidemiologists and infectious diseases specialists from Bel-

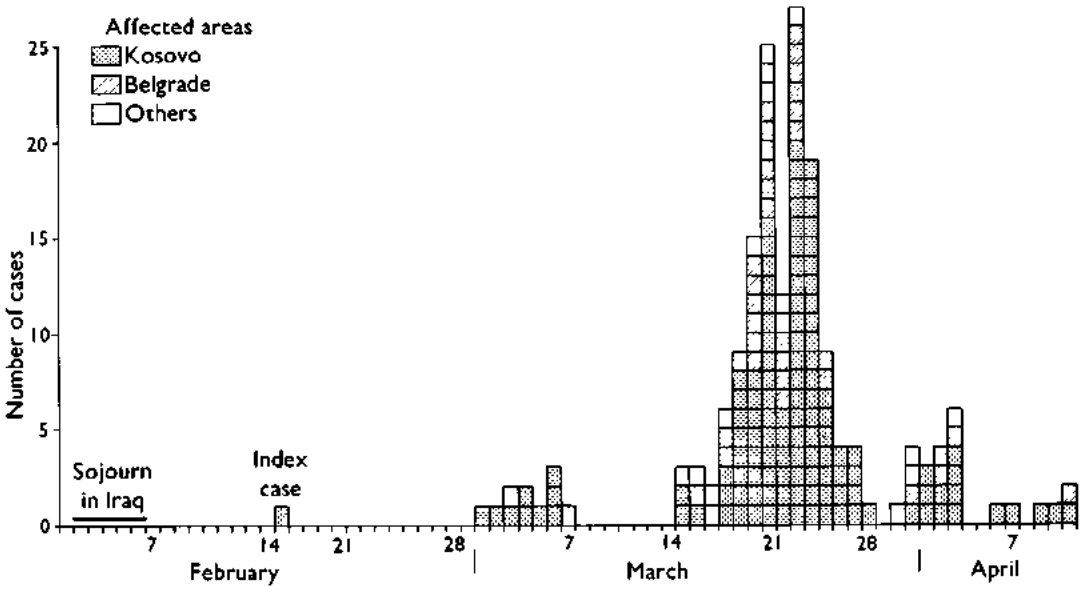


Fig. 23.7 Yugoslavia: number of cases of smallpox, by date of onset and locality, 1972. The first generation of cases occurred in Kosovo province and adjacent areas; the large second generation in Kosovo, Belgrade and some other places.

grade went to Kosovo and joined local health staff in clinical examinations and epidemiological investigations.

The Province of Kosovo, bordering on Albania, was then a rural, relatively undeveloped area, whose Albanian-speaking inhabitants regarded outsiders with suspicion. The population was composed of large extended families, whose members constantly visited one another, and the men frequently travelled long distances to look for work. Most of the epidemiologists carrying out the field investigations had to communicate through an interpreter with a rather uncooperative population, and this caused them some difficulties. The index case, for instance, never admitted to having had a rash and it was some time before circumstantial epidemiological and serological evidence confirmed the diagnosis of smallpox. The reticence of the man concerned was understandable. He belonged to the semi-secret Bektachi religious sect and was most reluctant to have his illness associated with the pilgrimage or to discredit his religion thereby. Indeed, had he been identified as the source of an infection which had killed several members of his village and of surrounding villages, his life might have been in danger.

Vaccination of the population in the initial foci in Kosovo began on 16 March and was extended in concentric rings, until by the end of the month almost all the population in the affected province had been vaccinated. There were problems, however, with coverage and unsuccessful vaccination owing to the use of liquid vaccine. It was not until the end of April that 95% successful coverage was achieved. By the third generation of the outbreak, most cases were occurring among persons who had been unsuccessfully vaccinated.

Containment measures in the 25 localities in villages and towns in which cases of smallpox had been detected included the strict isolation of patients, quarantine of their contacts in facilities specially established in hospitals, hotels, pensions etc., and vaccination of the population. In households in which more than one family member had been infected, their home was turned into a quarantine centre. Where necessary, whole villages were put under surveillance, the inhabitants' temperatures were taken and the skin of patients was inspected regularly. Population movement to affected areas was restricted and public meetings were prohibited.

In Kosovo, extensive vaccination of hospital staff and the general population was begun as soon as the diagnosis of smallpox had been confirmed, and the same procedure was

adopted for all 25 smallpox foci. The Federal Epidemiological Commission then decided to undertake a mass vaccination programme throughout the country. In 3 weeks, 18 million out of a total population of 20.8 million were vaccinated.

The epidemic, which caused 175 cases and 35 deaths, was brought under control 6 weeks after the first diagnosis of smallpox. Surveillance for the next 4 weeks having revealed no other case, Yugoslavia was declared free of smallpox on 9 May 1972.

Plate 23.5. Control measures taken during the 1972 outbreak in Yugoslavia. **A:** More than 300 health teams, some of them army medical units, took part in the vaccination campaign. **B:** Protective clothing worn by medical personnel in emergency smallpox hospitals. **C:** Check-points were established at hundreds of places along the main roads to check vaccination certificates.

It is interesting to note that there was an unusually high proportion of haemorrhagic-type cases: 10% as opposed to the usual 1%. Hospital transmission accounted for 48% of the infections. A high rate of transmission (an average of 12.8 new infections per case) during the second generation of cases was assumed to be associated with inadequate protection from vaccination, 37% of these cases having occurred among previously vaccinated persons. While the number of deaths among previously vaccinated persons was half that among the unvaccinated, the overall case-fatality rate was 20%. The age distribution of cases corresponded with that of the population affected, and the sex ratio was 57% males to 43% females.

The unusual magnitude of the outbreak was considered to be due to the sizeable proportion of susceptible individuals in the population, delayed diagnosis, hospital transmission, the initially large number of unsuccessful revaccinations, communication problems in the tracing of contacts, and an atypical haemorrhagic-type case, which gave rise to the extraordinarily high number of 38 secondary infections.

The spread of smallpox in south-western Asia in 1970–1972 and its importation into Yugoslavia and the Federal Republic of Germany embarrassed several of the countries involved and retarded the progress of the global eradication programme. However, they did help to mobilize support for the programme and to reinforce surveillance efforts in all the countries of south-western Asia.

LABORATORY-ASSOCIATED OUTBREAKS IN THE UNITED KINGDOM

Microbiological laboratory space inevitably becomes contaminated with the bacteria or viruses in use, the more easily if safety measures are not taken (see Chapter 30). Smallpox laboratories were no exception. However, the regular vaccination and revaccination of persons in any way associated with these laboratories provided good protection against their infection with variola virus.

In countries that still had endemic transmission of smallpox, it was only when cases occurred among laboratory workers that it was possible to ascribe them with any certainty to an infection acquired in a laboratory. Although laboratory-associated outbreaks of smallpox may have occurred in various countries of the Americas, Asia and Europe when the disease was endemic in them, only 3 known laboratory-associated outbreaks and 1 suspected outbreak have been recognized; they all occurred in the United Kingdom after smallpox had ceased to be endemic there (Table 23.11). Only 2 of these were fully documented: one in London (1973), the other in Birmingham (1978). A single-case outbreak in Liverpool, in 1949, involved a laboratory worker who was accidentally infected with variola virus while handling contaminated materials (A. W. Downie, personal communication, 1980). An outbreak of variola minor in the Midlands and Wales in 1966 was later associated with infection acquired from a laboratory. The 2 confirmed outbreaks will be described first.

Table 23.11 Laboratory-associated outbreaks of smallpox in the United Kingdom

Year	Locality	Numbers of Cases	Numbers of Deaths	Source
1949	Liverpool	1	0	Liverpool Medical School laboratory
1966	Midlands and Wales	72	0	Birmingham Medical School laboratory[a]
1973	London	4	2	London School of Hygiene and Tropical Medicine laboratory
1978	Birmingham	2	1	Birmingham Medical School laboratory

[a] Suspected.

The London Outbreak, 1973

This outbreak followed the last importation of smallpox into the United Kingdom, which occurred in February 1973, when an Anglo-Indian infected during a holiday in Calcutta became ill after his return to London at the end of February (No. 34, Table 23.2). There were no contact infections.

The laboratory-associated outbreak occurred in March and April 1973, during which another 4 cases of smallpox were reported in the United Kingdom (Cox, 1974). On 11 March 1973 a 23-year-old female laboratory assistant in the Mycological Reference Laboratory at the London School of Hygiene and Tropical Medicine became ill with influenza-like symptoms—headache, backache and high fever. She had been

vaccinated as a child and revaccinated in 1972, but did not recall noting any reaction at that time. On 13 March she visited her doctor, who assumed that she had influenza and treated her with oxytetracycline. On 15 March she developed a slight rash and a day later was admitted to St Mary's Hospital, London, with a provisional diagnosis of glandular fever, and placed in a general ward. A drug rash due to oxytetracycline was suspected and later, because she worked in a mycological laboratory, the possibility of fungal infection was considered.

On 22 March she was visited by a friend working in the mycology laboratory, who, at the request of the head of the laboratory, took scrapings from the patient's skin lesions, which were investigated the same afternoon. To the surprise of all, brick-shaped poxvirus particles characteristic of variola virus were seen with the electron microscope. An investigation of the patient's movements before the onset of fever revealed that on 28 February she had entered the poxvirus laboratory (located in the same building as the mycology laboratory) and had watched the chorioallantoic membranes of eggs inoculated with variola virus being harvested on the open bench.

The poxviruses being studied in the laboratory at that time included variola major virus (Harvey strain) and two strains of "whitepox" virus (see Chapter 30). Subsequent investigations showed that it was the Harvey strain of variola virus with which the technician had been infected (Dumbell, 1974).

The patient was taken to Long Reach Isolation Hospital in Dartford, Kent, and the diagnosis of smallpox was confirmed. As many identifiable contacts as possible were traced, vaccinated and placed under surveillance. Unfortunately this group did not include a woman who had occupied the bed next to the laboratory technician's until 20 March, at St Mary's Hospital, nor her son and daughter-in-law, who had often visited her in the general ward. On 30 March the 34-year-old son and his 29-year-old wife fell ill with a headache, back pain and nausea. On 2 April their condition deteriorated and they were admitted to an isolation ward of the West Hendon Hospital with a provisional diagnosis of viral gastroenteritis. A skin rash developed on 3 April and became vesicular a day later, when smallpox was suspected and confirmed by laboratory examination. On the same day both patients were transferred to the Long Reach Isolation Hospital and died, the wife from haemorrhagic-type smallpox and the husband from confluent ordinary-type smallpox.

On 24 April another case, diagnosed as variola sine eruptione, was notified in a nurse, successfully vaccinated on 4 April, who had tended the couple with smallpox in the West Hendon Hospital. A week later, she had fever accompanied by headache, backache and shivering, with a papular rash on her hands. She was transferred to Long Reach, where a diagnosis was made on the basis of the clinical history.

Thus, the "escape" of variola virus from the London poxvirus laboratory resulted in 4 cases, of which 2 were fatal. The British government set up a committee of inquiry, whose report (Cox, 1974) concluded that the technician had probably been infected by the respiratory route while watching the harvesting of chorioallantoic membranes from eggs on 28 February, and that the other 2 patients had been infected on 17 March, when visiting the hospital.

The important feature of the report, in the light of later actions about methods of handling variola virus in laboratories, is the description of the laboratory facilities used at that time. The report noted that the laboratory was of an old-fashioned design, grossly overcrowded and poorly equipped. Work with variola virus was done on an open bench and a deep-freeze for storing variola virus stood in the corridor. But, as Dr K. R. Dumbell of St Mary's Hospital Medical School testified, the conditions which prevailed there were comparable with those in other teaching hospitals and medical schools in London. Even as recently as 1973, then, scientists working with variola virus did not handle it as a highly dangerous agent but relied on good microbiological techniques and on the regular vaccination of all personnel involved in the laboratories rather than on physical safety facilities. This did not apply to laboratories specially built for handling dangerous microbial pathogens, such as the Microbiological Research Establishment at Porton Down, Wiltshire, in which elaborate physical facilities were provided for the safe handling of dangerous viruses and bacteria. The report concluded with a recommended Code of Practice for Safety in Laboratories Handling Variola Virus (see Chapter 30).

The Birmingham Outbreak, 1978

Ten months after the last case of endemic smallpox in the world had been detected in Somalia in 1977, the British health authorities reported to WHO that on 27 August 1978, a 40-year-old Englishwoman had been confirmed to be suffering from smallpox. The patient, Mrs Janet Parker, a medical photographer in the Anatomy Department of the Medical School of the University of Birmingham, became ill with fever, headache and muscular pains on 11 August and developed a rash on 15 August. This was at first thought to be a drug rash. She remained at her own home until 21 August, when she was transferred to her parents' house. On 24 August the appearance of vesicles led to a suspicion of smallpox, the patient was admitted to the East Birmingham Hospital and when a diagnosis of smallpox was confirmed by electron microscopy, she was placed in the Catherine-de-Barnes Isolation Hospital. Variola major virus was isolated from vesicle fluid on 27 August. Her condition, complicated by renal involvement, deteriorated rapidly and she died on 11 September.

Mrs Parker had last been vaccinated in 1966. She had not travelled abroad in the recent past and to the best of her knowledge had had no contact with any persons recently returned from abroad. Indeed, endemic variola major had not been present anywhere in the world since October 1975.

In order to investigate the matter, a Source of Infection Committee composed of 5 experts was established by the University of Birmingham on 28 August 1978. One of the members was Professor Henry S. Bedson, Head of the Department of Medical Microbiology of the Medical School of the University of Birmingham, in which the smallpox laboratory functioned as the regional diagnostic smallpox laboratory. Bedson was an active participant in WHO's coordinated laboratory investigations of variola and "whitepox" viruses (see Chapter 30). The committee suspected that the smallpox laboratory was the probable source of infection.

Meanwhile the health authorities had identified about 290 persons who might have had contact with the patient during her illness. These included the immediate members of her family and other relatives, patients of the East Birmingham Hospital, and colleagues at the Medical School. All were vaccinated and placed under surveillance at

Impact of the Birmingham Outbreak

In July 1978 there was a growing belief that the last case of smallpox in the world had occurred in Somalia in October 1977. It was not surprising, therefore, that the Birmingham incident led to a great deal of publicity in the media and caused considerable concern in the medical community throughout the world. Health administrators in the developing countries of Africa, in particular, renewed their calls for the cessation of laboratory studies of variola virus and the destruction of all stocks of the virus.

Because of the publicity, WHO received inquiries from the press and from health administrators in many countries concerning proposals for reducing the risk of another escape of variola virus from a laboratory. Information officers were recruited by the Smallpox Eradication unit to handle the inquiries, and Arita, as chief of the unit, developed plans to deal with the situation. Two meetings were convened: a meeting of experts in February 1979 to evaluate the justification for retaining variola virus stocks in laboratories, and a conference in April with the directors of 9 laboratories which were then retaining the virus, together with representatives of the governments concerned, to discuss control measures and future actions.

The plans were debated at a special open meeting held during the sixty-third session of the Executive Board in January 1979, which was attended by a large number of journalists, and the meetings took place as scheduled. Thus the Birmingham laboratory-associated outbreak, though an unfortunate incident, hastened a recognition of the risk of holding variola virus stocks and led to an immediate reduction in the number of laboratories retaining the virus, from 13 in 1978 to 7 in 1979 (see Chapter 30, Table 30.7).

home. Four of them were hospitalized with different illnesses, none of which was smallpox. Three were discharged from hospital, while the fourth person—the 77-year-old father of the deceased patient—developed fever on 1 September, 12 days after his daughter had been brought to his house in his car in the vesicular stage of her illness. He did not develop a rash but died suddenly on 5 September from a heart attack. The tragedy was not over. On 2 September the 49-year-old Professor Bedson was found severely ill after an apparent suicide attempt and died 5 days later. On 7 September Mrs Parker's mother, aged 70, became ill while in quarantine at home and on 8 September developed a sparse macular rash, which was confirmed by laboratory examination as being due to smallpox. She recovered and was discharged from isolation on 22 September.

In view of the mildness of the illness which the second patient developed, as well as the vigorous surveillance and control measures, a further community-wide spread of smallpox was judged to be very unlikely. Priority vaccination was restricted to contacts, persons who worked or lived in nearby foci and persons who needed vaccination to travel.

On 30 August 1978, the Secretary of State for Social Services requested Professor R. A. Shooter to conduct an official investigation, the results of which were published in July 1980 (Shooter, 1980). Dr Joel Breman, from the WHO Smallpox Eradication unit, participated as an observer in the first 3 meetings of this investigation. As in the episode in London in 1973, the index case was in a person not directly connected with work in the smallpox laboratory. Mrs Parker was a medical photographer who worked in another department of the medical school, though in rooms on the floor immediately above the smallpox laboratory (Plate 23.6).

The team of investigators inspected the premises thoroughly, carried out tests on air movement between the laboratory and the photographer's room and made exhaustive inquiries to determine whether there might have been personal contact between Mrs Parker and any worker in the virus laboratory during the last week of July.

It concluded that Mrs Parker had been infected with a strain of smallpox virus used in the smallpox laboratory, probably during the last week of July 1978, but how the virus was transferred to Mrs Parker was less certain.

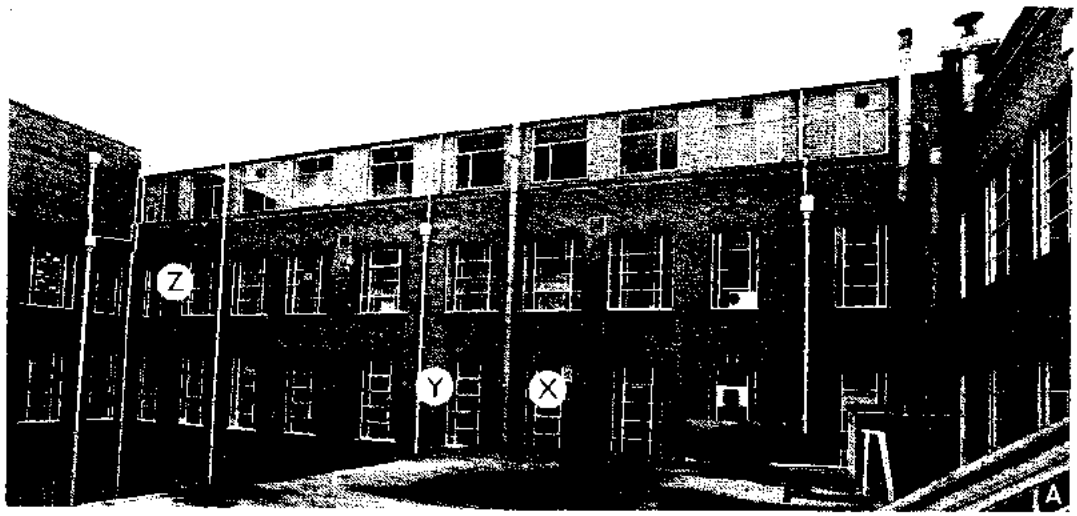
"The evidence points to two possible routes by which smallpox virus was transmitted from the pox laboratory to Mrs. Parker: by the airborne route, either through the duct in the 'telephone room' or while visiting the Medical Microbiology corridor; or by the personal contact route, transfer being by the visitor from the Medical Microbiology Department who regularly entered the animal pox room. We are unable to say with certainty which of these two routes might have led to Mrs. Parker contracting smallpox. Both are possible though neither seems capable of delivering a large dose of virus unless an accident occurred involving the liberation of virus, which was not recognised or recalled. Nevertheless, from what we know small doses of virus could have been liberated from time to time which could have been responsible for Mrs. Parker's infection. We believe that the airborne route through the duct to the 'telephone room' is the most probable way by which Mrs. Parker was infected because this seems to be the one route that could have selectively affected her." (Shooter, 1980.)

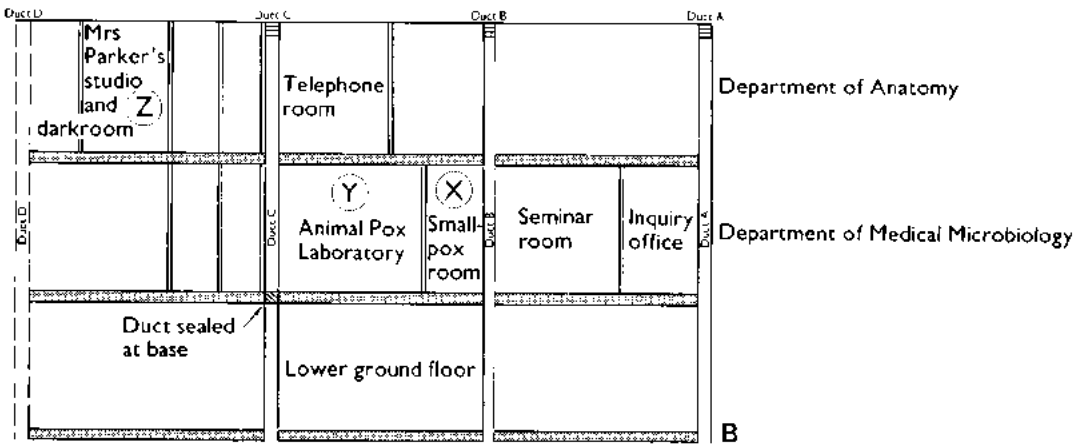
This episode constituted the last known outbreak of smallpox in the world, and Mrs Parker's mother the last known case of smallpox in the world. It is ironic that when cases of variola major had occurred again, they had emanated not from a remote source in Africa or Asia, but from a well-equipped laboratory in one of England's largest cities. As a consequence of this episode, much attention was paid to the problem of variola virus stocks in laboratories, a matter which actively interested many Member States at the Thirty-second and Thirty-third World Health Assemblies in 1979 and 1980 respectively (see Chapter 30).

Outbreak of Variola Minor in the Midlands and Wales, 1966

During the official inquiry into the Birmingham outbreak, the similarity of the apparent origin of an outbreak of variola

Plate 23.6 (opposite). Departments of Anatomy and Medical Microbiology at the Medical School, University of Birmingham. **A:** From the east courtyard. X = smallpox room; Y = animal poxvirus laboratory; Z = photographic studio. **B:** Diagram showing location of these rooms and the service ducts running through them. **C:** Photograph of the animal pox laboratory looking towards duct C, which is marked by the letter C. (From Shooter, 1980, with permission from the Controller of Her Majesty's Stationery Office, United Kingdom.)


Z
Y
X
A


Duct D
Duct C
Duct B
Duct A
Mrs Parker's studio and darkroom
Z
Telephone room
Department of Anatomy
Y
Animal Pox Laboratory
X
Small-pox room
Seminar room
Inquiry office
Department of Medical Microbiology
Duct sealed at base
Lower ground floor
B

C

minor in England and Wales in 1966 was brought to the attention of the team of investigators. The first case in this earlier outbreak to be identified and reported to WHO, on 2 May 1966, was in an unvaccinated 17-year-old girl who had developed an influenza-like illness on 16 April. Four days later a rash appeared, and she was admitted on 25 April to the Moxley Infectious Diseases Hospital, Walsall, Lancashire, as a case of chickenpox. Four days after that, smallpox was suspected and the girl was admitted to a smallpox hospital on 29 April. The diagnosis was confirmed by the isolation of variola minor virus.

Investigation of the girl's family and associates led to the discovery of an additional 71 cases of variola minor in the Midlands and Wales between February and August 1966. Detailed inquiries held in 1966 had failed to establish the source of infection. However, 12 years later, the team of investigators headed by Professor R. A. Shooter carried out a retrospective examination of all available reports and correspondence concerning the 1966 outbreak (Shooter, 1980). The earliest case identified was in an unvaccinated 23-year-old photographer employed at the Medical School of the University of Birmingham. He had become ill on 18 February with fever, headache and backache and had developed a generalized rash 4 days later. During the first week of illness he had remained at home and when the rash had appeared he had returned to work. He denied having had any contact with a person exhibiting a rash similar to his or with any recent immigrants or travellers from abroad. He himself had never been outside the United Kingdom. The relevant feature disclosed during the Shooter investigation was that the photographer had worked in the same studio and darkroom of the Medical School of the University of Birmingham as those used by Mrs Parker.

Eleven days before the index case of the 1966 outbreak became ill, work was being carried out with variola minor virus in the Birmingham smallpox laboratory, on the floor below (see Plate 23.6). Thus the photographer might have been infected, 12 years earlier, by the same route as Mrs Parker; hence the inclusion of this outbreak in Table 23.11 as "suspected" laboratory-associated.

The photographer became ill between 4 and 20 March 1966; his fiancée, his parents and a schoolteacher were infected at a folk-dance evening, and a 72-year-old man during a visit to a public house. These secondary cases gave rise to 2 main chains of transmission. The first spread from the photographer's fiancée to members of a youth club in her town and from them to their families and associates. The other chain stemmed from the 72-year old man, who infected 2 of his grandchildren, who in turn infected their friends and families. The spread continued, and at least 25 persons had been infected before 29 April, when the diagnosis of smallpox was made in the 17-year-old girl mentioned earlier. By June, 47 smallpox cases had been reported in the heavily populated West Midlands. Subsequently, new foci of infection appeared in Wales and Lancashire, although no connection could be established between these outbreaks and those in the Midlands, probably because of missed cases wrongly diagnosed as chickenpox.

The last known case occurred in Salford, Lancashire, with onset on 9 July 1966. The patient concerned was discharged from the isolation hospital on 1 August, but in compliance with the International Sanitary Regulations England and Wales were not declared free of smallpox until 18 August of that year. The reaction of the public and the health authorities to this outbreak differed greatly from the response, described earlier, to importations of variola major into European countries. Many cases in the 1966 outbreak had been misdiagnosed as chickenpox, and even when the health authorities became involved, they had not been particularly diligent in searching for cases and isolating and vaccinating contacts. The possible origin of the outbreak was not elucidated until the striking resemblance of the occupation and place of work of the first case to those of the index case in the laboratory-associated outbreak in Birmingham in 1978 became apparent.

CONCLUSIONS

Smallpox importations into European countries emphasized the risk of infection to which professional staff and patients in hospitals and other medical institutions were exposed. Over half of all cases associated with importations were found in this group, whose protection by regular vaccination with potent vaccine could have reduced the number of cases very substantially. Nevertheless, the

majority of the outbreaks were effectively controlled by surveillance and containment, and smallpox importations caused few disastrous events in Europe.

The review of importations into south-western Asia, especially the epidemic in 1970–1972 that spread from Afghanistan into Iran, Iraq and the Syrian Arab Republic and eventually into Europe, demonstrates that poor surveillance, and especially the deliberate suppression of reports of the disease, had extremely serious consequences both for the countries concerned and for their neighbours.

For most of the period after 1950, the Indian subcontinent was the major source from which smallpox was occasionally transferred to the countries of Europe, especially the United Kingdom and the Federal Republic of Germany, and to non-endemic countries in Asia. The majority of importations into Europe were due to Europeans returning home after travelling in the Indian subcontinent. In spite of the large volume of air traffic between the Indian subcontinent and the USA during this period, there were no importations into the latter country, possibly because of the better vaccination status and stricter enforcement of health regulations in the USA than in Europe.

As countries in Africa and South America became free of smallpox, they experienced importations mainly from one country in each of these continents with a large population and extensive endemic foci, which became the major exporter of smallpox to its neighbours—namely, Ethiopia in Africa and Brazil in South America.

The number of diagnosed laboratory-associated outbreaks was remarkably small, probably because of the high level of vaccination among laboratory staff. However, the last tragic incident in Birmingham emphasized the need for close supervision of variola virus stocks during the period following eradication.

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CHAPTER 24

THE CERTIFICATION OF ERADICATION: CONCEPTS, STRATEGY AND TACTICS

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INTRODUCTION

On 8 May 1980 delegates to the Thirty-third World Health Assembly, representing all 155 Member States of the World Health Organization, unanimously accepted the conclusions of the Global Commission for the Certification of Smallpox Eradication (World Health Organization, 1980), namely that:

(1) Smallpox eradication had been achieved throughout the world.

(2) There was no evidence that smallpox would return as an endemic disease.

The first conclusion was based on the findings of a series of independent international assessments, undertaken under WHO's auspices, of the efficacy of smallpox eradication programmes and surveillance in countries throughout the world, especially those in which smallpox had been endemic in 1967 and others at special risk. These activities constituted the programme for the "certification" of smallpox eradication. The second conclusion was founded on epidemiological investigations and research studies carried out during the course of the Intensified Smallpox Eradication Programme and summarized in Chapter 30.

Certification of the eradication of smallpox was possible because the virus had no animal reservoir, subclinical infections were rare and did not result in subsequent transmission, and latent infections did not occur. Just as the strategies and tactics used in the eradication of smallpox in different countries evolved over time (see Chapters 9 and 10), so also did the strategies adopted for certification increase in rigour and sophistication.

The present chapter describes these changing strategies and tactics, culminating with the declaration of global smallpox eradication at the World Health Assembly in 1980. The actual operations involved in the 79 countries in which special measures were taken are described in the following three chapters, which deal in turn with the activities of international commissions for the certification of smallpox eradication between 1973 and 1977 (Chapter 25), the varied activities outlined by the Consultation on the Worldwide Certification of Smallpox Eradication in 1977 and supervised by the Global Commission for the Certification of Smallpox Eradication (Chapter 26), and the final certification operations in the world's last stronghold of smallpox, the Horn of Africa, and in the world's most heavily populated country, China (Chapter 27).

HISTORICAL DEVELOPMENT OF THE CONCEPT OF CERTIFICATION

As outlined in Chapter 9, programmes to eradicate specified human diseases from particular localities, and eventually globally, date from the early years of the 20th century. Apart from Jenner's prophetic but hardly practical pronouncement in 1801 (see Chapter 6, Plate 6.8), the first explicit statement about the possible large-scale eradication of a human disease was a comment by Gorgas (1911a) on the eradication of yellow fever, a disease later (1915) nominated for global eradication by the International Health Commission of the Rockefeller Foundation (see Chapter 9). With the realization in the mid-1930s that there was an animal reservoir of the yellow fever virus (Soper, 1936), global eradication of that disease ceased to be a tenable objective. It was replaced by the idea of eradicating its urban vector, *Aedes aegypti*, from countries in the Americas, a concept that gained acceptance in 1942 partly because of the successful eradication of the imported African malaria vector, *Anopheles gambiae*, from Brazil in 1940 (Soper & Wilson, 1943). With these programmes of vector eradication came the need for some means of assessing whether the mosquito in question had indeed been eliminated from particular localities, regions and countries. The first "certification" procedures for *Aedes aegypti* eradication were developed by the Pan American Health Organization in 1954, revised in 1960, and issued in a definitive form in 1971 (Pan American Health Organization, 1971b). The criteria called for the absence of *Aedes aegypti* from a region for a period of at least 1 year, during which 3 surveys confirming the absence of the mosquito had been made. The final survey had to be carried out with the cooperation of the Pan American Health Organization, which provided the technical personnel needed for the task. If the survey confirmed the absence of *Aedes aegypti* mosquitos, the country was entered on the Pan American Health Organization's registry of countries considered free of this species.

When the malaria eradication programme was begun by WHO in 1955, it was realized that some mechanism was needed for convincing those outside the regions and coun-

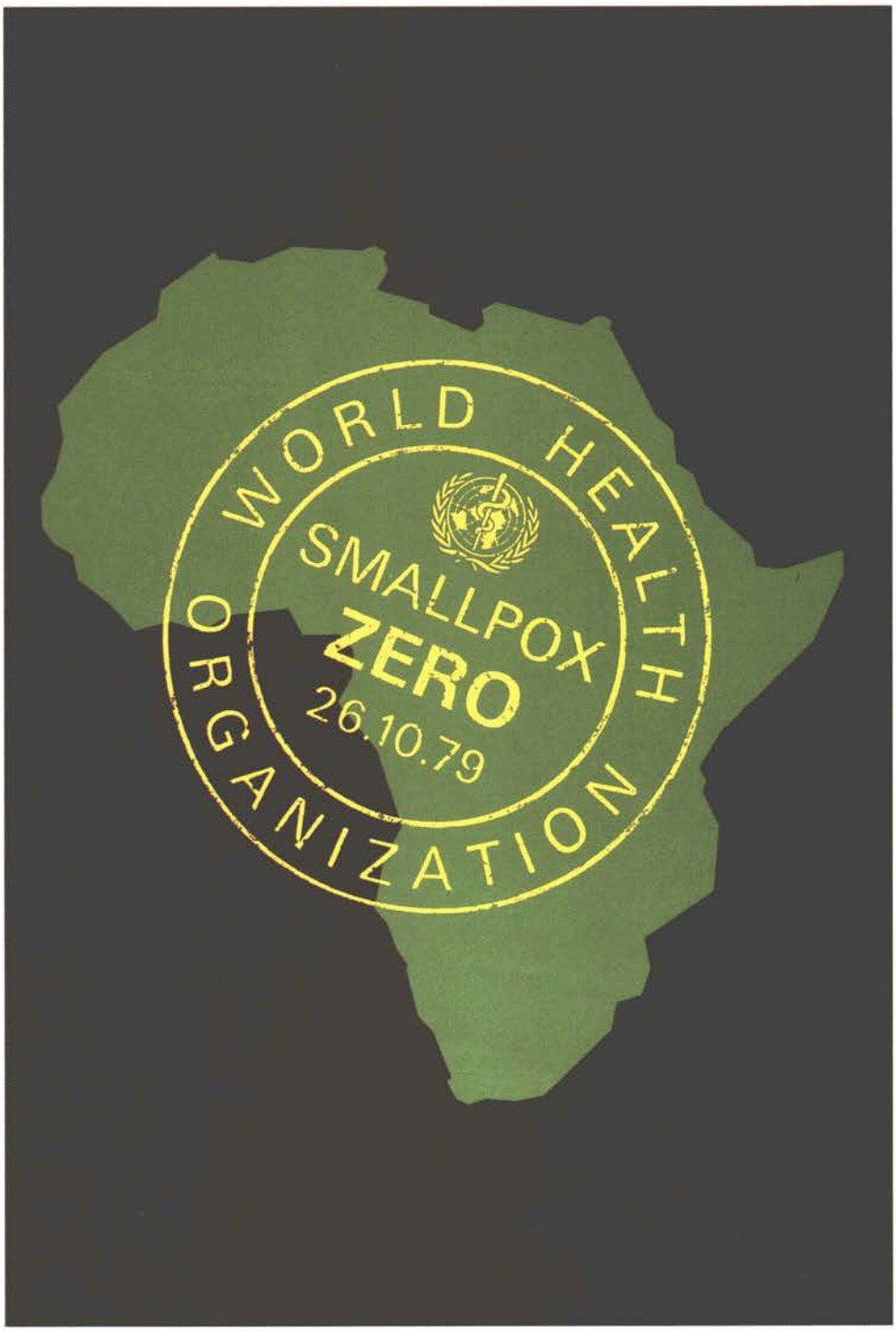


Plate 24.1. Poster produced in the 6 official languages of WHO on the occasion of the certification of the eradication of smallpox from the Horn of Africa on 26 October 1979, exactly 2 years after the world's last case of endemic smallpox occurred in Somalia.

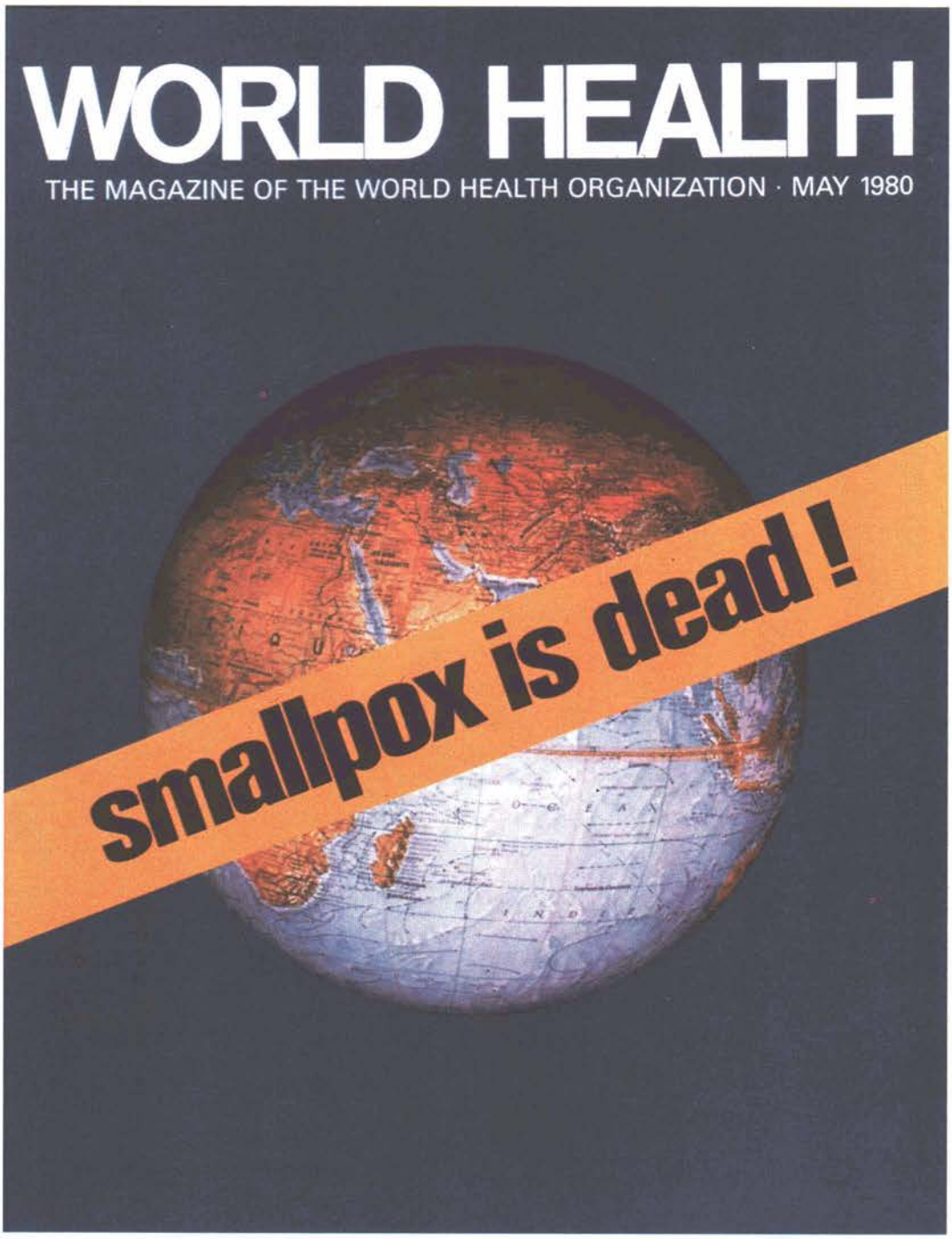


Plate 24.2. A complete issue of the WHO magazine *World health* was devoted to smallpox eradication at the time of the Thirty-third World Health Assembly's formal declaration that eradication had been achieved.

tries concerned that they were free of the disease. In 1960, the Thirteenth World Health Assembly requested the Director-General of WHO "to establish an official register listing areas where malaria eradication had been achieved, after inspection and evaluation by a WHO evaluation team". The methodology and procedures for certification were laid down in 1961 (WHO Expert Committee on Malaria, 1961) and amplified in 1966 and 1974. The essential feature of the assessment procedure was that a regional WHO evaluation team would visit the area for which registration had been requested by a government, analyse the epidemiological and operational data collected during the consolidation phase (a period of 3 consecutive years, during which no evidence of transmission had been found and during the last two of which no general measures of anopheline control had been practised), and examine the organization, methodology and quality of the surveillance operations and the plans for their maintenance. Each WHO evaluation team included at least one member of the WHO Expert Committee on Malaria, together with staff from the relevant WHO regional office or short-term consultants appointed by it. National experts from the country being assessed were not included, but the team relied heavily on briefing by them. The team's report was first reviewed at the WHO regional office and later by the WHO Expert Committee on Malaria, and on the latter's recommendation the area was entered in the official register.

With the imminent eradication of smallpox from South America in 1971, it became necessary for WHO, through its Smallpox Eradication unit, to develop procedures for the assessment of the claim that smallpox had been eradicated from the Americas. The earlier eradication programmes had established the important principle that it was not possible for any independent authority, such as a team of WHO experts, acting entirely on its own, completely to confirm the status of a country or region in respect of *Aedes aegypti* or malaria for any definite period of time. Instead, it was necessary for it to depend on records compiled by the national authorities, the quality of which could then be determined by field appraisal undertaken by a team of experts from outside the country.

The global eradication of smallpox, if it could be achieved, would be uniquely different from that of *Aedes aegypti* or malaria since two valuable but expensive public health measures could then be abolished: routine vaccination of populations in all countries and the requirement that international travellers had to be vaccinated. For this to be possible, however, the world community of public health officials and medical scientists would have to be convinced that global eradication had really been achieved. Assessment of the situation in each country therefore needed to be carried out by teams of highly respected scientists and health officials, independent both of the national authorities of the country being assessed and of WHO, which might be regarded as having a vested interest in the results. Having established the goal of global eradication—never a realistic objective in the case either of *Aedes aegypti* or of malaria—the Smallpox Eradication unit saw that the independence of the assessment teams needed to be placed beyond all possible doubt.

With these requirements in mind, a strategy for the certification of smallpox eradication was developed by the unit. This consisted first of the preparation of detailed "country reports" by the national health authorities of the countries concerned, assisted by WHO staff and consultants. The reports outlined the procedures by which it was believed that smallpox had been eliminated and described the capability of the surveillance system to detect cases of suspected smallpox. When the Smallpox Eradication unit judged that these preparations had reached an appropriate stage, arrangements were made for a group of independent international experts, who constituted what came to be called an "international commission for the certification of smallpox eradication", to visit the country or countries concerned. Their task was to study the country report, make visits wherever they thought necessary, assess carefully the capability of the surveillance system to detect cases of smallpox should they have occurred, and make recommendations about public health activities relevant to smallpox. This was a new strategy designed to solve the novel problem of convincing the international community that smallpox, formerly a universal disease, had been eradicated from particular countries, regions, continents and finally the world. On the basis of experience of the best tactics for particular situations, the certification process was modified and improved, but the essential features—adequate preparations and detailed documentation of the evidence of freedom

from smallpox for at least 2 years, and the independence and authority of the certification team—remained unchanged throughout.

ERADICATION: DEFINITION AND CRITERIA

To understand the way in which certification of smallpox eradication evolved, it is necessary to examine the definition of, and criteria for, eradication developed in 1967 by the WHO Scientific Group on Smallpox Eradication (1968) and ratified and slightly elaborated in 1971 by the WHO Expert Committee on Smallpox Eradication (1972).

From the time of WHO's foundation in 1948, the control of smallpox had been a matter of concern both to the World Health Assembly and to the WHO Secretariat. The concept of the global eradication of smallpox, as distinct from control within Member States, was first enunciated by WHO in 1958 and accepted as WHO policy by the Twelfth World Health Assembly in 1959 (see Chapter 9). The Intensified Smallpox Eradication Programme was launched in 1967 (see Chapter 10). Between these two dates, 1959 and 1967, the concept of the way in which eradication could be achieved underwent a very important change.

Definition in Terms of Vaccination Programmes (1962)

In 1962, in his report on smallpox eradication to the Fifteenth World Health Assembly (document A15/P&B/18; unpublished), the Director-General of WHO defined eradication by stating that: "From a practical viewpoint, countries in which smallpox has recently been persistently present may consider the disease to be eradicated when no cases of smallpox occur during the three years following the end of a satisfactory vaccination programme." In suggesting a period of 3 years, the Director-General was probably influenced by the use of this period in certification procedures for malaria eradication.

Definition in Terms of the Interruption of Transmission (1968–1980)

The first meeting of the WHO Expert Committee on Smallpox was held in Geneva in 1964. The WHO smallpox eradication programme was discussed (WHO Expert Committee on Smallpox, 1964), but no attempt was made to define specific criteria for eradication. However, in 1967 a meeting of the WHO Scientific Group on Smallpox Eradication (1968) specified the basic definition of, and the criteria for, eradication. Meeting in 1971, with 4 years' experience of the Intensified Smallpox Eradication Programme, the WHO Expert Committee on Smallpox Eradication (1972) confirmed both the definition and the criteria, although it stated them in slightly different terms.

The definition produced by the Expert Committee was subsequently endorsed without change by the Consultation on the Worldwide Certification of Smallpox Eradication in 1977 and by successive meetings of the Global Commission for the Certification of Smallpox Eradication in 1978 and 1979. Because they were formulated later, we shall use the 1971 definition of the criteria for eradication (WHO Expert Committee on Smallpox Eradication, 1972) as the basis for discussion:

> "Eradication of smallpox is defined as the elimination of clinical illness caused by variola virus. Since smallpox is transferred direct from man to man in a continuing chain of transmission, and since there is no human carrier state of epidemiological importance and no recognized animal reservoir of the disease, the absence of clinically apparent cases in man may be assumed to signify the absence of naturally occurring smallpox.
>
> "In order to be able to confirm the interruption of smallpox transmission an effective surveillance is needed so that clinical infections can be detected. Recent experience indicates that, in all countries with a reasonably effective surveillance programme, residual foci can be detected within 12 months of apparent interruption. Thus, in countries with active surveillance programmes, at least 2 years should have elapsed after the last known case—excluding well-defined and contained importations—before it is considered probable that smallpox transmission has been interrupted.
>
> "Because of the ease with which smallpox can be transmitted from one country to another, the concept of 'eradication' can apply only to a continent. Thus, although smallpox may be considered to have been eradicated from certain continents, it cannot yet be said to have been eradicated from Africa, Asia, or South America.
>
> "On the basis of epidemiological and technical considerations and the considerable experience

acquired so far, the Committee believes that the global eradication of smallpox, as defined above, is possible."

Since the foregoing formulation of "eradication" became the basis of the whole certification process, several aspects of it warrant comment and explanation.

Disease or virus

In the first paragraph the phrase "Eradication of smallpox is defined as the elimination of clinical illness..." provides the most important criterion; this could be used because, as already pointed out, there was no animal reservoir, subclinical infections were rare and epidemiologically unimportant, and latent infections did not occur. It was therefore logical to base a certification programme on the results of campaigns of active surveillance, which could detect only manifest disease. It would be impossible to use such a criterion for diseases such as plague or tuberculosis.

Furthermore, this criterion took into account the difference between interrupting person-to-person transmission of smallpox and supplementing this by the destruction of all variola virus stocks, as some experts had urged. Achievement of the interruption of human transmission throughout the world was a practical and verifiable goal; ensuring the destruction of all variola virus stocks, in the deep-freeze cabinets of every laboratory in every country of the world, was impracticable and unenforceable.

Period of freedom from smallpox

In the second paragraph, the stipulation that "... in countries with active surveillance programmes, at least 2 years should have elapsed" before certification could be undertaken, proved to be a conservative but manageable criterion for determining the timing of certification activities, although the choice of a period of 2 years was an arbitrary one. It had been adopted by the 1967 meeting without much discussion, and by 1971 further experience of eradication programmes suggested that it was realistic. In all countries in which WHO-assisted programmes were implemented, the surveillance systems improved greatly during such programmes and, in the great majority of countries, no outbreaks of smallpox had occurred after transmission was thought to have been interrupted. There were, however, a few exceptions. In Brazil, Indonesia and Nigeria, outbreaks were discovered 10–34 weeks after transmission was thought to have been interrupted, but in no case was the stipulated period of 104 weeks even remotely approached. After these incidents, countries in which national eradication programmes were still in progress further strengthened their surveillance systems. The effectiveness of such systems was always evaluated by WHO before a date was fixed for the visit of an international commission.

In a practical sense, the reliability of certification was related to two factors – namely, the lapse of time since the last known case and the intensity of surveillance. If the intensive surveillance in operation during the eradication campaign had been maintained for 2 years thereafter, this period was more than long enough to judge whether or not eradication of the disease had been achieved. Where longer periods had elapsed, a less sensitive surveillance system was sufficient to detect the serial transmission of smallpox since many hundreds of cases would need to occur to maintain the chains of transmission. Because the supply of susceptible subjects would soon be exhausted, smallpox could not persist for prolonged periods in sparsely populated inaccessible regions; and in towns and cities, in which the population density was high enough to support continued transmission, large numbers of cases could not go unobserved. After eradication had been achieved in the Indian subcontinent, the Smallpox Eradication unit believed that, in countries in which active surveillance had been maintained after an energetic eradication campaign had been successfully completed, the interval could well be reduced from 2 years to 1. However, to make assurance doubly sure, it was decided to adhere to the earlier decision.

Importations and laboratory-associated outbreaks

The second paragraph of the definition of eradication excludes "well-defined and contained importations". Apart from importations by travellers from endemic countries into countries in which transmission had been interrupted, as occurred in Europe, the Americas, Africa and Asia (see Chapter 23), this exclusion was used by the Global Commission as a basis for its decision regarding the status of the last cases of smallpox in the world. This outbreak, which occurred in

Birmingham, England, in August September 1978, was associated with variola virus being used for experimental work in the virology laboratory of the University of Birmingham (see Chapter 23). The United Kingdom had been free of endemic smallpox since 1934, although there had been a number of importations from the Indian subcontinent after that date. This event, like the well-contained laboratory-associated outbreak in London in 1973, was regarded in the same manner as an importation into a country that had long been free of endemic smallpox. It was a tragic and potent reminder of the risks of working with variola virus with anything except the strictest containment facilities (see Chapter 30), but it was in no way a threat to the eradication programme.

The outbreaks in China in the mid-1960s, which resulted from the activities of variolators but were not reported to WHO until 1984 (see Chapter 27), could be regarded in the same light as a laboratory-associated outbreak.

Eradication as a "continental" concept

In the third paragraph, the statement that "the concept of 'eradication' can apply only to a continent" meant that the eradication of smallpox should not be certified when the endemic disease was absent in a single country or even a group of adjacent countries, but only on a continental or global basis. The practice developed of using the terms "interruption of transmission of smallpox" or "elimination of smallpox" to signify the achievement of smallpox-free status by individual countries.

In fact, the certification of eradication in an entire continent was possible only in the Americas. In Asia and Africa it proved impracticable to delay national certification until smallpox was eradicated throughout these continents. Thus in Asia, since there had not been a recorded importation of smallpox into Indonesia since 1949, certification was arranged in 1974, 2 years after the last reported case but before other Asian countries were smallpox-free. Certification of eradication in Africa posed special problems because of the persistence of smallpox in Ethiopia long after freedom from the disease had been achieved in western Africa. Certification activities were therefore not started in western Africa until 1976 and certification in other areas was undertaken in stages, both because of the shortage of personnel and time and because of the differing eradication programmes of African countries.

DEVELOPMENT OF STRATEGIES FOR CERTIFICATION

The occurrence of what was believed to be the last case of smallpox in Brazil (and thus in the Americas) in April 1971 forced the Smallpox Eradication unit to plan immediately the steps to be taken before eradication of smallpox from the Americas (in practice from South America) could be certified for acceptance by the international community, in 1973, 2 years after the last case. Two operations new to the unit needed to be planned and implemented: (1) the collection in South America of basic data for the assessment of the smallpox status of each country; and (2) the selection and mode of operation of the international assessment team, which in 1973 would examine the evidence collected during the preceding 2 years. The way in which these operations developed can best be appreciated by a consideration of certification procedures in 3 areas of the world—South America, Indonesia and western Africa.

South America

National preparations

In 1971 a general plan of work was outlined by agreement between WHO Headquarters and the Regional Office for the Americas. It called for specific reports on the smallpox status of all countries in South America except Chile, which, because of its geographical isolation, was judged to be at only slight risk of importations from Brazil or elsewhere, following its last case in 1954. WHO staff and consultants were assigned to visit the various countries, for most of which little information had previously been available, and were instructed to prepare detailed reports in line with requirements specified prior to their visits. While these assessments were being made, it became apparent that the surveillance systems in some of the countries were improving, and the data gathered became increasingly valuable as time progressed. Special programmes were undertaken for the

areas of greatest concern—e.g., the Amazon basin.

Because of the paucity of established health units in the Amazon basin and the inaccessibility of many of the areas of interest, special investigations were undertaken in parts of the basin within Bolivia, Colombia, Ecuador, Peru and Venezuela. The Brazilian parts of the basin were systematically and thoroughly searched by smallpox teams working with the malaria service; these teams progressed systematically through the entire area, vaccinating people wherever they were found and inquiring about smallpox. Other measures, outlined in Chapter 25, were also taken. Because only variola minor had been present in South America in recent decades, pockmark surveys would have been of little assistance, and none was attempted.

A mechanism of international assessment

Drawing primarily on the precedent of assessment of the malaria status of countries in which that disease was thought to be eradicated, the Smallpox Eradication unit proposed that the results of the reports provided by national authorities and WHO consultants should be evaluated by what came to be called an "International Commission for the Certification of Smallpox Eradication". The first such commission to be established, that for South America, suffered from defects in both its composition and its performance, which were largely remedied when the next one (for Indonesia) was set up and did not recur. In the first place, the Commission for South America included several persons who had been involved in the eradication programme in South America including as chairman, at the insistence of the Brazilian government, Dr Alfredo Bica, Secretary of Public Health of Brazil and formerly Director of the Communicable Diseases Division of the Pan American Sanitary Bureau/WHO Regional Office for the Americas. The Smallpox Eradication unit, for its part, failed to provide a detailed plan of action for the Commission. As a consequence, procedures and records and the history of smallpox eradication programmes in various countries were examined in a rather cursory and superficial manner. Finally, when the Commission framed its recommendations, it showed little appreciation of the significance of the eradication of smallpox from the Americas, calling for continued routine vaccination throughout the continent, as before. Fortunately for the reputation of the Commission, the Smallpox Eradication unit and WHO as a whole, subsequent history showed that smallpox had indeed been eradicated from South America.

Indonesia

The last case of smallpox in Indonesia occurred on 23 January 1972. Since there was no record of a case of smallpox having been introduced from the nearby endemic countries in Asia since 1949, it was judged appropriate to proceed with arrangements to certify eradication in Indonesia (as an isolated country) in 1974. In the light of the experience in South America, the methods of preparation for certification and for field activities by the members of the International Commission were strengthened.

National preparations

Like many other governments, that of Indonesia was not enthusiastic about continuing active surveillance after it was believed that smallpox had been eliminated and had to be persuaded of its importance. Then, sufficient data would need to be collected to satisfy the Commission that smallpox had been eradicated. Dr Paul Wehrle, an experienced smallpox consultant, therefore visited Indonesia in order both to identify weaknesses in the surveillance system, and to work with the government and WHO advisers to develop a plan which in his opinion would provide such data. Subsequently, health staff carried out intensive precertification activities, including an active search in high-risk areas and the collection of separate written declarations by the chiefs of tens of thousands of villages, stating that they had searched for smallpox throughout the area under their authority and had failed to find any cases.

Two factors which facilitated the preparations in Indonesia, compared with those in South America, were that pockmark surveys were useful because the prevailing variety of smallpox had been variola major, and that a reward was offered to anyone reporting a case of smallpox.

Selection of members of the International Commission

Profiting from the experience in South America, the Smallpox Eradication unit

modified the procedure for the selection of members of the International Commission, adopting an approach that was applied in the formation of all subsequent commissions. The major problem with the constitution of the South American Commission was that a national of the major country under examination, Brazil, was appointed chairman. This mistake was never repeated, but after a good deal of debate Dr Julie Sulianti Saroso, Director-General for the Control and Prevention of Communicable Diseases in the Indonesian Ministry of Health, was made a member of the Indonesian Commission. Subsequently nationals of the country concerned were appointed to an international commission only in special circumstances—as in India, where this was necessary to enable the Commission to have access to Bhutan. Governments of neighbouring countries (Australia and Malaysia) were asked to nominate representatives, on the grounds that these countries were most at risk of importations should smallpox still be present in Indonesia so their nationals might be expected to be especially critical of the material presented. In general, the Smallpox Eradication unit took the view that the certification process would be best served by the appointment to each commission of individuals (whether from governments or universities) respected by their own governments so that their opinions on smallpox eradication would also be respected. Great care was exercised in the appointment of the chairman, and the precedent set in Indonesia, whereby Dr Wehrle visited the country during the preparatory period and subsequently acted as chairman of the International Commission, was followed in other countries in which certification was of great importance—e.g., Ethiopia and India. After eradication had been certified in Indonesia, the Smallpox Eradication unit tried to include in each new international commission one or two members who had already had experience with an earlier commission.

This Commission and all subsequent commissions were asked to reach one of two conclusions: either that they were satisfied that eradication had been achieved, or that they would be satisfied that eradication had been achieved if certain specific measures were undertaken. At the initial briefing session in Jakarta, the Australian and Malaysian members of the Commission were extremely doubtful whether eradication had been achieved in Indonesia. One observed that he had recently heard rumours of cases in northern Sumatra and the other believed that cases were almost certainly occurring in the slum areas of Jakarta itself. Such scepticism was welcomed by the Smallpox Eradication unit since, if these members were persuaded by the evidence presented in the course of the activities undertaken by the Commission itself, their conclusions would be more convincing to the international community.

A feature of the work of the Indonesian Commission was that Dr Sulianti Saroso, speaking as Director-General for the Control and Prevention of Communicable Diseases in the Indonesian Ministry of Health, concluded her opening remarks at the first session by saying that Indonesia was convinced that it was free of smallpox. Consequently, she invited members of the Commission to feel free to "go anywhere, with anyone, and make any inquiries" they chose to. This statement was honoured and provided an important precedent for other international commissions.

Western Africa

The last case of smallpox in western Africa occurred in Nigeria in May 1970 and United States bilateral assistance was terminated in 1972. At that time, however, smallpox was still endemic in many other parts of Africa and certification was therefore postponed. Smallpox was progressively eliminated from one African country after another, but the stipulation that eradication was a continental concept made the Smallpox Eradication unit reluctant to undertake certification in Africa. However, by 1975 endemic smallpox appeared to be limited to the Horn of Africa, and it was decided to initiate the certification process in the African continent in phased groups of countries so as to reduce logistic and administrative problems. The epidemiological situation in different parts of the African continent was nevertheless borne in mind. A group of 15 countries in western Africa was certified first because transmission had first been interrupted there and because they were furthest away from the areas in which smallpox was still endemic. Surveillance had been intensive in these countries for 2 years after the presumed elimination of smallpox, but had then very largely declined. Documentation on activities carried out since 1972 was comparatively sparse in most countries in the region. On the other hand, the long period of

time that had elapsed since smallpox had been seen in any country of western Africa provided good grounds for believing that the disease had been eliminated and had not been reintroduced. While notification systems were not as well developed as might have been desired, they had been capable of detecting cases of monkeypox in human beings in 1970 and succeeding years, as well as outbreaks of unusual and extremely serious diseases, such as Lassa fever or Ebola virus disease, which had come to the notice of local health staff within 6 months and of central health personnel within 12 months of their occurrence. If smallpox, especially variola major, had occurred in western Africa after 1970, it seemed reasonable to expect that the health staff of the country concerned would have known about it within a year. The 6-year interval since the last case thus provided a very large safety margin.

Because the Commission's visit took place so long after the last known case, many national smallpox eradication staff, as well as United States epidemiologists who had worked in the programme, had long since left and taken up other employment. Moreover, the Commission had to deal with 15 countries covering a vast area—almost two-thirds of the size of the USA—in which the health services infrastructure was much less well developed than in South America or Indonesia. To cope with this situation, WHO regional staff and consultants made frequent visits to these countries and two important changes were made in the procedure. First, preparations for certification were simplified, compared with the elaborate precertification searches and detailed documentation that were used in Indonesia and subsequently in the Indian subcontinent. Preparation of the country reports was based on a standardized questionnaire developed by the Smallpox Eradication unit; when completed, this provided essential information about the national eradication campaign. Secondly, a new method of active search was developed for use in all areas in which variola major had occurred—namely, large-scale facial pockmark surveys in children (see later in this chapter). It was reasoned that, if these surveys included all children up to 15 years of age, there would be some who had had smallpox when it was still endemic and would have pockmarks which the teams should detect. This served as an internal control in the survey, in that failure to detect any individuals with pockmarks would call into question the work of the team concerned. When children with pockmarks were detected, efforts were made to find out in which year they had contracted the disease that had caused the scarring. Such information was surprisingly easily obtained from most villagers. The age of the youngest pockmarked child also provided objective evidence as to when smallpox had last occurred.

Western Africa was certified to be free of smallpox on 15 April 1976, and in May 1976 the Twenty-ninth World Health Assembly, commenting for the first time on the certification process, endorsed "the procedures developed by the Director-General in the use of groups of international experts in the certification of eradication and [asked] for the full cooperation of all countries concerned in carrying out these procedures, so that countries throughout the world may have confidence that eradication has been achieved" (resolution WHA29.54). The successful carrying out of certification in western Africa provided the experience necessary for the staff of WHO and various national health authorities to proceed with certification in other areas of Africa as well as in south-western Asia.

Coordination of Certification Activities

In consultation with staff from the appropriate regional office and the national smallpox eradication programme, the Smallpox Eradication unit was responsible for deciding whether a particular country was ready to receive an international commission and, if so, when. This obviously required frequent visits by WHO smallpox eradication staff and, on occasion, by WHO consultants, to countries preparing for certification. Thus, even though smallpox had been eliminated from all countries except Somalia by the end of 1976, a number of WHO smallpox eradication staff were retained or recruited to assist in the certification process. From 1977 onwards, the Smallpox Eradication unit in Geneva consisted of Arita, who replaced Henderson after his departure in February 1977, Dr Joel G. Breman, an epidemiologist from the Center for Disease Control, Atlanta, USA, with extensive experience in smallpox and tropical diseases, Dr Alexander Gromyko, Dr James Tulloch and Mr John Wickett. Dr Celal Algan, Dr Ziaul Islam, Ježek, Dr Daniel Tarantola and Dr Lev Khodakevich assisted

the programme as WHO staff members in the regional offices.

Certification of smallpox eradication was not solely a technical matter but also involved many managerial and political questions. Ladnyi, who had acted as WHO intercountry smallpox adviser in eastern Africa from 1965 to 1971, returned to WHO Headquarters in 1976 as an Assistant Director-General and remained in this post until 1983. In this capacity he was able to help to solve some of the political problems that inevitably arose during the organization of certification activities.

The support provided by WHO staff and consultants was of two types. First, in a country in which an eradication campaign had been developed and executed with the active participation of WHO staff epidemiologists or consultants, some international personnel continued to work with national staff after eradication in organizing and assessing the active searches for unreported cases of smallpox, as well as in pockmark surveys or in the surveillance of chickenpox cases. The last-named activity was carried out in a number of countries, being of special importance where variola minor had been endemic, since this disease rarely left pockmarks and was readily confused with chickenpox. Secondly, in countries of western, central and southern Africa, in which the eradication campaign had been organized many years before certification and in which WHO or outside epidemiologists were not involved in continued surveillance, special arrangements were made to assign experienced WHO consultants or staff epidemiologists from either inside or outside the country to assist the health services in precertification activities.

In countries from which smallpox had recently been eradicated great interest was shown in certification, whereas in those in which the disease had been eliminated many years before, certification was not considered by the national health administrators to be of high priority. In some countries, national health officials who had taken part in the national smallpox eradication campaign had risen in the local health service hierarchy and were important in persuading senior government administrators of the importance of certification. The assignment of special WHO consultants and epidemiologists also helped to promote certification activities.

To persuade governments to mobilize adequate numbers of staff to prepare properly for certification, several approaches were used: (1) WHO regional office and Headquarters staff communicated with countries by letter or memorandum, emphasizing the importance of certification if the final achievement of smallpox eradication was to be accepted by the world community; (2) further encouragement was provided through coordination meetings with representatives of the countries concerned and through visits by staff of the Smallpox Eradication unit; and (3) WHO funds were frequently provided to cover fuel and vehicle repair costs and the living expenses of national surveillance teams.

J. KUMAZAWA, 1980

Plate 24.3. Joel G. Breman (b. 1936) was a medical officer with the WHO Smallpox Eradication unit, 1977–1980, during the most active part of the certification programme, and participated in monkeypox surveys in western and central Africa. He also worked as an epidemiologist in the eradication campaign in western Africa, 1967–1969.

NATIONAL PREPARATIONS FOR CERTIFICATION

The methodologies employed in national preparations for certification (precertification activities) differed according to the variety of smallpox present in the countries concerned and whether eradication was followed immediately by post-eradication surveillance and preparation for certification, or precertification activities were carried out many years after the occurrence of the last known case of smallpox. In most cases the final product was a "country report" that was

assessed by the appropriate international commission or the Global Commission.

The WHO Scientific Group on Smallpox Eradication (1968) had pointed out the need for an effective surveillance system capable of detecting and investigating suspected smallpox cases in order to demonstrate that smallpox transmission had been interrupted. Although all countries in which smallpox had been endemic continued some form of smallpox surveillance after the date of onset of what they considered to be the last case, its intensity differed substantially from country to country. In the last countries to be affected by smallpox, such as Bangladesh, Ethiopia, India and Somalia, the national programmes continued active post-eradication surveillance that was even more intensive than during the eradication campaign itself. The documentation in such countries was more complete than that available elsewhere and these countries could be visited by international commissions just 2 years after they had reported their last case. On the other hand, in most countries of Africa, special surveillance programmes had ceased long before certification was undertaken. In all cases, country reports covered the following items, which are described more fully later:

(1) a description of the routine reporting system;

(2) an account of special active searches, both in high-risk areas and throughout the country, including the methods of assessing the quality of the searches;

(3) the results of pockmark surveys, if appropriate;

(4) a description of chickenpox surveillance, wherever it was undertaken;

(5) the status of rumour registers, in which all suspected cases of smallpox were recorded, and sometimes also cases with fever and rash;

(6) a list of specimens sent for laboratory investigation and the test results;

(7) an account of the publicity given to the need for reporting smallpox cases, the rewards offered for finding a case (where appropriate), and public awareness of such rewards;

(8) documentation on other precertification activities.

Effectiveness of the Routine Reporting System

Each country provided data on the number and distribution of health units, including the number and types of hospitals, health centres or stations and peripheral health units, with maps showing their distribution throughout the country, and on the regularity and completeness with which they reported. The number of monthly or other periodic reports called for was compared with the number actually received. Data were also supplied on the reporting of cases of chickenpox, especially those with a fatal outcome. Finally, records of the action taken when a suspected smallpox case was reported were examined. During visits by WHO consultants in preparation for certification, action was taken to increase awareness among health personnel of the need to report immediately any cases where smallpox was suspected.

Active Searches for Unreported Cases

In most countries, specially organized mobile teams conducted field surveys in order to obtain up-to-date information regarding activities in connection with smallpox. The teams were organized and directed by the national smallpox eradication programme (when still operative), by those who had been involved in the eradication programme during its active phase, or by those responsible for the communicable diseases programme.

Special investigations were carried out in localities in which the risk of unreported smallpox was thought to be greatest. These included areas in which the last known outbreaks had been notified, those in which suspected smallpox cases or chickenpox deaths had been reported after the last known outbreak of smallpox, and those in which health coverage and communications were poor. Areas bordering on countries in which smallpox had recently been endemic, or in which there had been recent extensive population movements, were also included. Special attention was given to the villages in which the last known cases had occurred. Such investigations provided information as to the effectiveness of control measures and case detection during the concluding phase of the programme in the country. If it was found that all cases in an outbreak had been detected and containment was satisfactory, this increased confidence in the efficacy of the surveillance–containment activities.

A general survey was usually planned for cities, towns, and larger villages, since experience had shown that, if smallpox had per-

The Absence of Evidence is not Evidence of Absence

From the beginning of the global eradication programme, steps were taken to encourage the submission of all reports of smallpox in any country thought to be free of the disease and to investigate all such reports. There had always been serious doubts with smallpox, as with cholera, whether the absence of reported cases really meant that the disease was absent from the country concerned. Reports of suspected cases of smallpox in non-endemic countries had been queried by the Smallpox Eradication unit since the Intensified Smallpox Eradication Programme began, in order to determine definitely whether or not they were imported cases or whether they represented continuing endemic transmission. As the campaign progressed, such reports took on a greater significance and eventually in 1978 an international rumour register was established in Geneva (see Chapter 28). Rumours were very important. Thus, although no cases were officially reported from Iran after 1963, information that smallpox might be occurring there in 1971 was drawn to the attention of WHO by a WHO consultant as well as by a number of international staff working with other health agencies. Reports of imported cases in Somalia before 1976 were also received from embassies long before being notified officially by the government. Similarly, the serious outbreaks which occurred in the Salt Lake refugee camp in West Bengal in 1971 were unknown to the government and to WHO until reported by an American epidemiologist who had observed cases of smallpox in a television news film taken at the camp (see Chapter 15).

sisted in smaller villages or nomadic groups, it would ultimately reach the larger population centres. The localities to be visited were selected so as to include communities with health units and primary schools, since these attracted people from a large area who might report suspected cases. The usual objective was to reach a sufficient number of communities to ensure that at least 20–25% of the entire population of the country was covered by the survey.

In the countries which were the last to become free of smallpox—Bangladesh, Ethiopia, India, Nepal, Pakistan and Somalia—country-wide house-to-house searches to discover possible cases were conducted on several occasions. A large number of health staff, volunteers and temporarily recruited searchers were deployed so that the search could be completed within a period of 3–4 weeks.

Search teams were organized in order to obtain information about cases of smallpox and chickenpox, actual or rumoured, in primary schools, health units, markets and other places at which people congregated, from nomadic and other migratory groups, and on some occasions from all households in selected villages or urban areas. Their training covered the following aspects:

(1) The status of smallpox eradication in the country, including details of the last outbreaks, suspected cases, and deaths from chickenpox, and an indication of particular localities requiring special investigations and field surveys.

(2) The characteristic features whereby facial pockmarks caused by smallpox could be distinguished from scars caused by other conditions. In this connection, it was emphasized that only persons with facial pockmarks caused by smallpox or suspected smallpox were to be investigated and the findings documented.

(3) Techniques for the epidemiological investigation of suspected cases, including the collection of specimens for laboratory investigation.

(4) Methods to be used in selecting the itinerary for field visits and the recording and reporting of data.

The organization of active searches in various countries is described in detail in subsequent chapters. One universal and important feature on which WHO consultants and staff preparing for certification insisted, however, was that the effectiveness of the searchers themselves should be properly assessed by follow-up staff whose task was to

Plate 24.4. Facial pockmarks. **A**: Moderately severe in a Nigerian girl 7 years after an attack of smallpox. **B**: Severe, in an Afghan who had suffered from smallpox many years before.

evaluate the work done by visiting houses and villages selected at random from among those previously visited by the search teams. Special assessment teams directed by national programme staff were organized for this purpose and each month visited up to 10% of the places previously visited in the course of the searches.

Pockmark Surveys

Permanent facial pockmarks were found in about 70% of those who survived Asian variola major, the rates being slightly lower after infection with the somewhat less virulent forms of variola major virus found in some parts of Africa. Heavy diffuse facial scarring, readily observed at a distance of 5 metres, was seen on the faces of many victims, but others had lesser degrees of scarring that could be detected only by close inspection. Residual pockmarks, which tended to flatten out over time, were found less frequently among those infected during the first few years of life. The presence of 5 or more depressed facial scars 2 mm or more in diameter at the base was accepted as indicating a probable previous attack of smallpox (see Plate 24.4) and such persons were carefully interrogated to determine the time of occurrence of the illness and its cause. Contrary to what might be expected, it was found that, as mentioned before, most villagers generally remembered precisely when an individual had acquired the disease which caused the scars. Chickenpox also sometimes leaves residual scars, but it was unusual to find 5 or more scars on the face. Facial scarring or pitting resulting from other causes, such as burns and acne and other skin diseases, could usually be distinguished by experienced observers, but these cases too were investigated by interrogation and, where possible, by review of the medical records.

Variola minor, which was prevalent in Brazil and in several parts of Africa during the period of the Intensified Smallpox Eradication Programme, caused far less scarring. A careful follow-up study in Somalia (Ježek & Hardjotanojo, 1980) showed that 5 or more facial pockmarks could be detected in only 7% of patients seen 1 year after recovery. Pockmark surveys were of little use and were not carried out in countries such as Brazil, Ethiopia and Somalia, in which only variola minor had occurred in recent years. A number of African countries had experienced both

variola major and variola minor and in many the pockmark surveys were supplemented by surveillance of cases of chickenpox (see below).

When a pockmarked person was found, the dating of his illness became a matter of importance; if it was more recent than the last known case of smallpox, the adequacy of the surveillance system was open to question. The surveys concentrated on the examination of children, as their illnesses were usually more recent than those of adults. Failure to find pockmarks in any children born since the occurrence of the last known case in the country provided important evidence that transmission of variola major had been interrupted.

A widely varying incidence of pockmarks was observed in pockmark surveys carried out by national teams in 34 African and 5 Asian countries. A relatively high incidence was found in schoolchildren in some countries, particularly where large outbreaks of variola major had occurred a few years before transmission had been interrupted. However, when the date of illness of each case was carefully investigated, no children were found whose illness was more recent than the last reported case.

In many countries the members of the international commission also carried out pockmark surveys during their field visits. The prevalence of facial pockmarks which they observed was often higher than that recorded during the national surveys, since they tended to focus on high-risk areas, such as those in which the last known cases of smallpox had occurred.

Chickenpox Surveillance

Where variola minor was prevalent and residual pockmarks were uncommon, emphasis was placed on the surveillance of chickenpox cases, which were sometimes clinically confused with smallpox. It was thought that a surveillance system sensitive enough to detect a large proportion of chickenpox cases would, in all likelihood, detect smallpox, if it were present. Efforts were made to verify the diagnosis of a number of such cases, especially those which were severe or fatal, by the examination of scabs or vesicular fluid in the laboratories of WHO collaborating centres.

Both the fixed and the mobile health units sought to discover and report chickenpox cases. In addition, some countries introduced the notification of chickenpox during the post-eradication period where previously this had not been required. The taking of specimens from at least one case in each outbreak, especially if a death had occurred, was requested and specimens were also obtained from patients who had not been vaccinated against smallpox and those with an extensive rash involving the palms and soles. In a few countries, a small reward was offered for the discovery of the first case of chickenpox in a previously unrecognized outbreak.

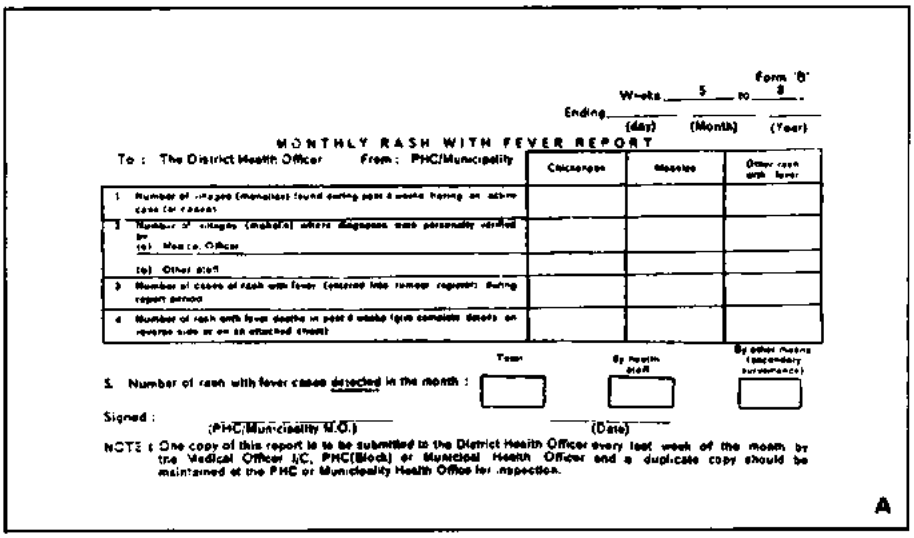
Rumour Register

In 1974, a new device was introduced in India—a register in which all cases of smallpox were recorded, and later all cases of fever with rash. It was particularly effective in countries in which smallpox was then endemic—namely, certain Asian countries and in the Horn of Africa. Rumour registers (Plate 24.5) were maintained at both national and lower levels. At the regional level, health officials kept a record of all patients, including the full name, age, sex, village or locality, presence or absence of a vaccination scar, date, and data relevant to the illness. All cases entered in the register were investigated by qualified personnel. If there was any doubt regarding the diagnosis, a consultation was sought through the national surveillance organization and specimens were collected. All the information supplied by the regions was recorded in national registers.

Specimens for Laboratory Diagnosis

Relatively few specimens were collected when smallpox was widespread because the diagnosis was usually obvious; if there was any doubt, cases were treated as smallpox. As the incidence fell to low levels, increasing numbers of specimens were taken and, as transmission came closer to being interrupted, specimens were collected from each suspected case.

In countries in which variola minor had been endemic, preparing for certification required the collection of large numbers of specimens from patients with chickenpox and with other types of fever with rash, and from other patients in whom smallpox was suspected. They were sought over a wide geographical area and especially in population



Form 'B'

Weeks 5 to 8

Ending (day) (Month) (Year)

MONTHLY RASH WITH FEVER REPORT

To : The District Health Officer From : PHC/Municipality

	Chickenpox	Measles	Other rash with fever
1 Number of villages (Municipal wards) found during past 4 weeks having an active case (or cases)			
2 Number of villages (Municipal wards) where diagnosis was personally verified by (a) Medical Officer			
(b) Other staff			
3 Number of cases of rash with fever (entered into rumour register) during report period			
4 Number of rash with fever deaths in past 4 weeks (give complete details on reverse side or on an attached sheet)			

5. Number of rash with fever cases detected in the month :

Total	By Health staff	By other means (secondary surveillance)

Signed : (PHC/Municipality M.O.) (Date)

NOTE : One copy of this report is to be submitted to the District Health Officer every last week of the month by the Medical Officer I/C, PHC(Block) or Municipal Health Officer and a duplicate copy should be maintained at the PHC or Municipality Health Office for inspection.

A

GOVERNMENT OF INDIA
National Smallpox Eradication Programme

WORLD HEALTH ORGANIZATION
Global Smallpox Eradication Programme

DISTRICT MONTHLY REPORT OF FEVER WITH RASH CASES

DISTRICT_____ STATE_____ MONTH_____ 197 WEEK NO :____ TO NO : _____

REPORTING OFFICER, NAME_____ POSITION_____

TOTAL NUMBER OF REPORTING UNITS :____ NUMBER OF REPORTS RECEIVED : _____

BASIC REPORTING UNITS (PHC, Municipalities, Hospitals, etc.)	NUMBER OF CASES OF RASH WITH FEVER ENTERED INTO RUMOUR REGISTER				SMALLPOX	NUMBER OF CHICKENPOX				NUMBER OF MEASLES				NUMBER OTHER RASH WITH FEVER			
	Total	Through Market Searches	During Search Week	Other means (Secondary Surveillance)	Suspected cases (Containment Initiated)	Outbreaks	Cases	Deaths	Outbreak verified By MOs	Outbreak verified By Others	Outbreaks	Cases	Deaths	Outbreak verified By MOs	Outbreak verified By Others	Outbreaks	Cases	Deaths	Outbreaks verified By MOs	Outbreaks verified By Others
TOTAL																				

NOTE: Month should include the weeks according to international allocation of weeks (inside of front cover of the yellow reporting booklet).

Within five days after the last day of month, send a copy of this report to State NSEP Office.

B

Plate 24.5. Forms (rumour registers) used for reporting cases of fever with rash in India. **A:** At primary health centres. **B:** At district offices; the district reports were consolidated at the state level on similar forms.

Table 24.1 Country of origin and number of specimens tested by the WHO collaborating centres in Atlanta and Moscow between 1969 and 1979[a]

Country	Number of specimens received (and number positive for smallpox)										
	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979
Africa											
Angola	0	0	0	0	0	0	0	0	1	98	23
Botswana	0	0	18 (14)	107 (56)	14 (5)	9	8	2	41	211	54
Burundi	0	3 (2)	0	5	4	3	1	0	0	0	0
Cameroon	0	6	3	0	21	12	9	19	10	1	14[b]
Central African Republic	0	0	0	3	0	0	0	0	0	0	5
Chad	0	6	4	0	0	0	0	0	0	0	0
Congo	0	0	0	70	0	0	0	0	2	1	0
Côte d'Ivoire	0	0	10[b]	4	32	5	4	1	0	0	0
Dahomey (Benin)	30	1	2	1	0	0	0	2	0	12[b]	0
Djibouti	0	0	0	0	13 (9)	7 (2)	0	0	17	67	75
Ethiopia	0	0	0	24 (23)	22 (5)	39 (9)	113 (33)	434 (60)	582	1 153	1 042
Ghana	30	15	15	12	0	0	0	0	0	0	0
Guinea	4 (1)	1	0	0	0	0	0	0	0	0	0
Kenya	0	0	12 (12)	6	2	9 (3)	2	1	147 (5)	126	1 473
Lesotho	0	0	0	0	0	0	0	0	0	32	27
Liberia	1	32[b]	143	5	0	1	1	3	0	0	0
Malawi	0	0	0	0	2	2	0	3	295	24	1
Mali	0	2	1	1	0	0	0	0	0	0	0
Mauritania	0	0	0	0	0	0	1	2	1	2	0
Mozambique	0	0	0	0	0	0	4	0	62	14	1
Namibia	0	0	0	0	0	0	0	0	0	9	9
Niger	22 (11)	8	8	4	2	0	0	1	0	0	0
Nigeria	250 (87)	108 (54)	187[b]	21	4	2	1	3	0	0	0
Rwanda	5 (5)	10 (9)	0	0	2	0	0	0	3	0	0
Senegal	0	0	0	0	0	0	0	1	0	0	0
Sierra Leone	5	24[b]	0	0	0	0	1	3	1	0	1
Somalia	0	0	0	0	0	0	0	56 (32)	865 (265)	1 623	1 271
South Africa	0	0	0	0	0	0	0	0	0	48	103
Southern Rhodesia (Zimbabwe)	0	0	0	0	0	0	0	0	0	23	0
Sudan	0	0	2 (1)	2 (1)	9	22	9	18	15	34	5
Swaziland	0	0	0	0	0	0	0	0	1	38	3
Togo	14 (2)	2	2	0	0	0	0	0	0	0	0
Uganda	0	0	0	5 (3)	0	0	1	1	0	119	0
United Republic of Tanzania	2 (1)	12 (5)	0	0	1	0	2	0	3	75	0
Upper Volta (Burkina Faso)	4	5	24	3	72	5	1	0	1	0	0
Zaire	0	23[b] (9)	167 (4)	142[b]	78[b]	63[b]	136[b]	104[b]	98[b]	101[b]	125[b]
Zambia	0	0	0	0	0	0	1	0	50	42	0

Americas											
Bolivia	1	0	4	0	0	0	0	0	0	0	0
Guyana	0	1	0	0	0	0	0	0	0	0	0
Nicaragua	0	0	0	0	1	0	0	0	0	0	0
Venezuela	0	0	4	1	0	0	1	0	1	0	0
Asia											
Afghanistan	0	0	0	0	4 (1)	0	1	0	4	0	0
Bahrain	0	0	0	0	0	0	0	0	0	51	1
Bangladesh	0	0	0	2 (1)	9	1 (1)	18 (3)	162	625	0	0
Burma	0	0	6	18	0	0	0	11	0	0	0
Democratic Yemen	0	0	0	1	0	0	0	1	0	30	7
Dubai	0	0	9 (7)	1	0	0	0	0	0	1	0
India	0	0	7 (5)	20 (15)	24 (14)	27 (20)	395 (126)	354	904	1	0
Indonesia	0	12	8 (6)	22 (9)	3	3	0	1	0	0	0
Iran	0	0	0	0	0	0	0	0	0	347	0
Iraq	0	0	0	0	0	0	0	0	0	13	1
Kuwait	0	0	0	0	0	0	0	0	0	78	4
Lebanon	0	0	0	0	1	0	0	0	0	0	0
Malaysia	0	0	1	0	0	0	0	0	0	0	0
Nepal	0	0	0	4 (1)	37 (27)	48 (40)	16 (8)	5	3	0	0
Oman	0	0	0	0	0	0	0	0	0	57	5
Pakistan	0	6 (5)	1	7 (6)	10 (5)	22 (11)	49	109	7	2	2
Qatar	0	0	0	0	0	0	0	0	0	23	0
Saudi Arabia	0	0	7	0	1 (1)	0	0	0	24	105	0
Sri Lanka	0	0	0	0	1 (1)	0	0	0	0	0	0
Syrian Arab Republic	0	0	0	3 (3)	0	1	0	0	0	9	4
United Arab Emirates	0	0	0	0	0	0	0	0	0	52	1
Viet Nam	0	0	0	0	0	1	0	0	0	0	0
Yemen	0	0	1	2	7	6	3	2	2	28	22
Europe											
Belgium	0	0	0	0	0	0	0	0	0	0	1
Italy	0	0	0	0	0	0	0	0	1	0	0
Switzerland	0	0	0	0	0	0	0	1	0	0	0
Total	368 (107)	277 (84)	646 (49)	496 (118)	376 (68)	288 (86)	778 (170)	1 300 (92)	3 766 (270)	4 650	4 280

[a] Recorded by date of receipt in Geneva. Includes only specimens for which testing results were reported. Includes multiple specimens from the same individual if taken. Excludes serum, animal, variolation and other specimens associated with special studies.

[b] Of which positives for monkeypox by year numbered: 1970 (Zaire 1, Liberia 4, Sierra Leone 1), 1971 (Côte d'Ivoire 1, Nigeria 2), 1972(5), 1973(3), 1974(1), 1975(3), 1976(3), 1977(7), 1978 (Zaire 8, Benin 1), 1979 (Zaire 4, Cameroon 2).

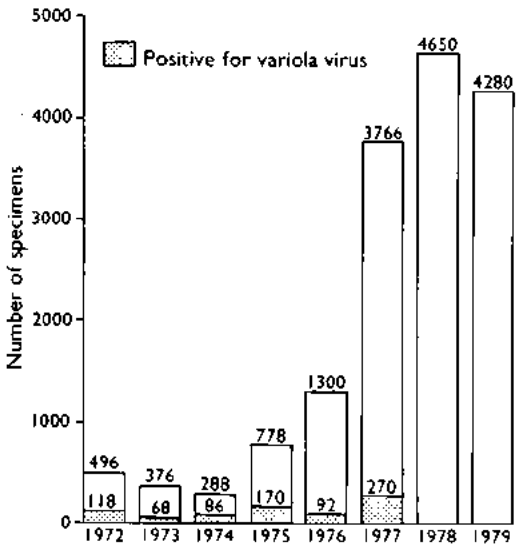


Fig. 24.1. Number of specimens collected from cases of smallpox, suspected smallpox, chickenpox, or suspected monkeypox and tested by WHO collaborating centres, 1972–1979.

groups and regions considered most likely to harbour smallpox. Specimens were forwarded to Geneva and from there sent either to the WHO collaborating centre in Atlanta or to that in Moscow. The specimens were shipped and tested with the least possible delay and those given priority were dealt with immediately, the results being cabled to the field.

Table 24.1 shows the national origin of specimens tested between 1969 and the end of 1979. The number tested rose from 288 in 1974 to over 4200 in 1978 and 1979 (Fig. 24.1). The percentage of specimens in which variola virus was found was relatively large during the earlier years, but none was positive after October 1977. About three-quarters of the specimens collected in 1978 and 1979 came from Ethiopia, Kenya and Somalia, which had reported their last cases (of variola minor) in 1976 and 1977 and were preparing for certification in 1979. Most specimens came from cases of chickenpox, the virus of which does not grow on the chorioallantoic membrane of the chick embryo. However, electron microscopy showed that many of them contained herpesvirus particles (varicella virus).

Publicity Campaigns and Rewards

Publicity campaigns aimed at encouraging people to report suspected cases and informing them that they would receive a reward if any of the cases turned out to be positive had been a feature of the eradication campaigns in the Indian subcontinent and the Horn of Africa and they continued until formal certification had occurred. In large urban centres, use was made of radio, newspapers, and television. In smaller villages and remote areas, leaflets and posters showing pictures of smallpox patients were more frequently used. Health unit personnel were encouraged to inquire about smallpox and other illnesses with fever and rash, and mobile teams repeatedly visited schools, markets and other places, where they informed the public about the disease, either in conversation or by loud hailer. In several countries so many posters and signs were fixed to walls that the smallpox teams were asked to desist because they were defacing the buildings.

The rewards were initially small but were gradually increased until they ultimately reached the sum of US$1000, offered by WHO in 1978 (Plates 24.6 and 24.7). In their contacts with schoolchildren or other segments of the population, active search teams showed the smallpox recognition card, asked people what the disease was, when cases had last been seen, and whether there were any reports or rumours of smallpox or chickenpox in the area. The teams also inquired whether people knew where to report if they did know of such a case and also whether they knew about the reward and its value. Since the value of the reward was changed at intervals, the replies provided an indication of how recently information had been received about the campaign.

The reward system was not readily accepted in all countries, since some national health authorities feared that it would establish a precedent with regard to the reporting of other diseases, although in fact no evidence of this was subsequently found. In western Africa, for example, the offering of rewards was discussed at the coordination meeting in 1975, during preparations for certification, but was finally rejected. However, rewards became an important method of surveillance, especially in Asian countries.

For smallpox transmission to have continued without detection when a large proportion of the population knew about the disease and the reward appeared highly unlikely. Thus, many countries conducted surveys to assess what proportion of the population knew about smallpox and where to report a

Rewards for Reporting Smallpox

The idea of offering a reward for information on cases that were proved to be smallpox originated in Indonesia, following the discovery that information on known smallpox cases had been suppressed by local officials because they feared punishment for failure to control the disease. It was taken up in most Asian countries in which smallpox was still endemic, and in some African countries. The reward was important in several areas of India, in which the reporting of cases by a health officer was taken as *prima facie* evidence that the vaccination campaign for which he was responsible had not been sufficiently thorough and he was punished for this by transfer or other means. By announcing that a reward would be given for reporting a case, the government made it quite clear that it wanted cases to be reported. Moreover, if health officers continued to suppress reports, lower-level staff anxious to receive the money bypassed them and reported the cases.

The size of the reward increased as the likelihood of finding a case of smallpox declined. The existence of a reward proved to be most effective in two ways: it increased the reporting of suspected cases of smallpox and, during active searches, questions aimed at discovering whether people knew of the reward proved an excellent method of assessing the effectiveness of search teams.

In April 1978, a coordination meeting was held in Nairobi, Kenya, to discuss preparations for the certification of the Horn of Africa. At that time 5 months had elapsed without a reported case of smallpox despite continuing surveillance in the Horn of Africa, as well as elsewhere in the world. One of the proposals discussed during the meeting was that a global WHO reward should be established to promote the reporting of smallpox. Reporters covering the meeting enthusiastically supported this idea. As a result of a recommendation from this meeting, the Thirty-first World Health Assembly in May 1978, in its resolution on smallpox (WHA31.54), requested the Director-General

"... to establish a reward of US$1000 for the first person who, in the period preceding final certification of global eradication, reports an active case of smallpox resulting from person-to-person transmission and confirmed by laboratory tests, in the belief that such a reward will strengthen worldwide vigilance for smallpox as well as national surveillance in priority countries".

Thereafter, the reward was widely publicized through radio, newspapers, television, etc., and a specially designed poster (Plate 24.7) was distributed to all countries. Immediately after the announcement of the award, many suspected cases were reported to WHO Headquarters, not only from developing but also from developed countries, including France and the USA. All proved to be false alarms. The reward was never collected.

case, or had heard about the reward. The surveys were often combined with active searches for cases of unreported smallpox. In the more populous and more recently endemic countries these campaigns reached a very high proportion of the people.

Documentation

Each country expecting to be visited by a commission was asked by WHO to prepare a comprehensive report ("country report") containing demographic data, information on its notification and surveillance system, a description of its smallpox eradication programme, information about the most recent outbreaks and data on precertification surveillance activities. These reports were submitted to the international commission at the beginning of its visit and provided the basic information needed for the planning of its field trips.

OPERATION OF INTERNATIONAL COMMISSIONS

The membership of all the international commissions is set out in Annex 24.1 and their operation is described in Chapters 25–27. General features of the method of selecting commission members, as developed after the certification of Indonesia, and their usual mode of operation, are outlined below.

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No. 30

WORLD HEALTH ORGANIZATION
GENEVA

ORGANISATION MONDIALE DE LA SANTÉ
GENÈVE

WEEKLY EPIDEMIOLOGICAL RECORD
RELEVÉ ÉPIDÉMIOLOGIQUE HEBDOMADAIRE

Epidemiological Surveillance of Communicable Diseases
Telegraphic Address: EPIDNATIONS GENEVA *Telex 27821*

Service de la Surveillance épidémiologique des Maladies transmissibles
Adresse télégraphique: EPIDNATIONS GENÈVE *Telex 27821*

Automatic Telex Reply Service
Telex 28150 Geneva with ZCZC and ENGL for a reply in English

Service automatique de réponse
Télex 28150 Genève suivi de ZCZC et FRAN pour une réponse en français

28 JULY 1978 — 53rd YEAR — 53e ANNÉE — 28 JUILLET 1978

SMALLPOX SURVEILLANCE — SURVEILLANCE DE LA VARIOLE

REWARD US$ 1 000 — RÉCOMPENSE

A reward has been established by the Director-General of WHO for the first person who, in the period preceding final certification of global eradication, reports an active case of smallpox resulting from person-to-person transmission and confirmed by laboratory tests.

(Resolution WHA31.54, World Health Assembly, 1978)

Le Directeur général de l'OMS a institué une récompense à attribuer à la première personne qui, au cours de la période précédant la certification définitive de l'éradication mondiale, signalerait un cas actif de variole résultant de la transmission d'un être humain à l'autre et confirmé par des essais de laboratoire.

(Résolution WHA31.54, Assemblée mondiale de la Santé, 1978)

SMALLPOX-FREE WEEKS WORLDWIDE **39** SEMAINES SANS CAS DE VARIOLE DANS LE MONDE

LABORATORIES RETAINING VARIOLA VIRUS

With the interruption of transmission of smallpox in the world population, the only remaining possible source of infection will be laboratories still retaining stocks of the causative virus.

Accordingly, the Thirty-first World Health Assembly (1978) has requested that all laboratories retaining variola virus, except WHO Collaborating Centres, destroy their stocks or transfer them to a WHO Collaborating Centre. Of at least 76 laboratories identified by WHO to have variola virus since all countries and areas were polled from 1975 to 1977, 57 had voluntarily transferred or destroyed their strains by the end of 1977. In 1978 five additional laboratories have disposed of their strains.

Instituto Adolfo Lutz, São Paulo (Brazil)
Laboratoire national de la Sante publique, Paris (France)
Microbiological Research Establishment, Porton Down, Salisbury (United Kingdom)
Virus Instituto Salud Pública, Lima (Peru)
Walter Reed Army Institute of Research, Washington (USA)

Currently there are at least 14 laboratories with variola virus *(Table 1)*. China reports that more than one laboratory has this virus.

Security measures for such laboratories were recommended by a "Workshop Meeting on Safety Measures in Laboratories Retaining Variola Virus", convened by WHO in August 1977. With continued cooperation the number of laboratories retaining variola virus will be further reduced to not more than four WHO Collaborating Centres by 1980.

LABORATOIRES DÉTENANT ENCORE DU VIRUS VARIOLIQUE

Avec l'arrêt de la transmission de la variole dans la population mondiale, la seule source possible d'infection sera constituée par les laboratoires détenant encore des stocks de virus pathogène.

Aussi la Trente et Unième Assemblée mondiale de la Santé (1978) a-t-elle demandé à tous les laboratoires, autres que les centres collaborateurs de l'OMS, détenant du virus variolique de détruire leurs stocks ou de les transférer à un centre collaborateur. Sur au moins 76 laboratoires identifiés par l'OMS comme détenant du virus variolique depuis l'enquête conduite de 1975 à 1977 sur tous les pays et circonscriptions, 57 avaient volontairement transféré ou détruit leurs souches à la fin de 1977. En 1978, cinq autres laboratoires se sont défaits de leurs souches, soit:

Instituto Adolfo Lutz, São Paulo (Brésil)
Laboratoire national de la Sante publique, Paris (France)
Microbiological Research Establishment, Porton Down, Salisbury (Royaume-Uni)
Virus Instituto Salud Publica, Lima (Pérou)
Walter Reed Army Institute of Research, Washington (EUA)

Actuellement, il existe au moins 14 laboratoires qui possèdent du virus variolique *(Tableau 1)*. La Chine signale que plus d'un laboratoire de ce pays détient le virus en question.

Un atelier sur les mesures de sécurité à appliquer dans les laboratoires conservant des stocks de virus variolique réuni par l'OMS en août 1977 a recommandé les mesures de sécurité à appliquer dans les laboratoires en cause. Grâce à un esprit de collaboration de toutes les parties, il n'y aura plus en 1980 que quatre laboratoires qui conserveront des stocks de virus variolique, il s'agira dans les quatre cas de centres collaborateurs de l'OMS.

Epidemiological notes contained in this number:

Adenovirus Infections, Legionnaire's Disease, *Neisseria gonorrhoeae*, Poliomyelitis Surveillance, Smallpox Surveillance, Surveillance of Animal Rabies, Surveillance of Nosocomial Infections, Viral Diseases Surveillance.

List of Newly Infected Areas, p. 228.

Informations épidémiologiques contenues dans ce numéro:

Infections à adénovirus, Maladie de l'*American Legion*, *Neisseria gonorrhoeae*, surveillance de la poliomyélite, surveillance de la rage animale, surveillance de la variole, surveillance des infections nosocomiales, surveillance des maladies à virus.

Liste des zones nouvellement infectées, p. 228.

Plate 24.6. The *Weekly epidemiological record* was used extensively to promote the certification activities by publishing pertinent information. The front page of the issue for 28 July 1978 announced the offer of a reward of US$1000 for reporting an active case of smallpox and recorded that 39 weeks had passed since the last case in the world. The front-page article reported on laboratories that had disposed of their stocks of variola virus; such stocks were by then considered the only possible remaining source of infection.

REWARD · RECOMPENSE
$1000
Smallpox Variole ОСПА Viruela Smittkoppor
The World Health Organization offers US $ 1000 to the first person reporting an active smallpox case resulting from human-to-human transmission and confirmed by laboratory tests. Valid until global eradication is certified.
L'Organisation mondiale de la Santé offre une récompense de US $ 1000 à la première personne qui signalera un cas actif de variole résultant d'une transmission d'un être humain à un autre et confirmé en laboratoire. Cette offre est valable jusqu'à la certification de l'éradication mondiale.
天花 चेचक Furuqa Ndui ፈንጣጣ الجدري

Plate 24.7. Poster produced by WHO in mid-1978, publicizing the reward of US$1000 for finding a confirmed case of smallpox.

Membership

The timing of the visits to the countries by international commissions and their membership were decided by WHO in the course of discussions with national health authorities. Individuals were selected who would be critical in their assessments and whose views as experts would be respected both nationally and internationally. Some of those selected were experts in communicable disease control, others in virology or health management. On each commission, one or two members were appointed from the countries most at risk of importation of smallpox from the country or countries to be certified. As time passed a deliberate effort was also made to include in the international commissions experts from as many different countries as possible, so that the nature and extent of the efforts made to document the interruption of transmission would be widely known. Special care was taken in the selection of the chairman. Apart from the first international commission, in South America, the chairman was not a national of any country under review and, after the certification of Indonesia, officials from the country concerned were, with few exceptions, excluded from the international commissions. Exceptions were made for the single group of experts who, as members of separate international commissions, certified Bangladesh and Burma respectively, by including a Burmese member in the commission assessing the adjacent country of Bangladesh and a Bangladeshi as a member of the commission assessing Burma. In addition, a senior Indian military medical officer was included in the Indian commission, so that visits could be made to areas to which foreigners did not have access at that time.

After the appointment of the Global Commission for the Certification of Smallpox Eradication early in 1978, its members served as chairmen or members of almost all of the international commissions. In this way members of the Global Commission became familiar with the certification process at the country and regional levels. In all, 76 experts from 48 countries served on international commissions (see Annex 24.1).

Mode of Operation

The principal aim of a commission's visit to a country was to evaluate the reliability of that country's report by interviewing health personnel and examining records at both central and peripheral levels, so as to ascertain whether smallpox transmission had been interrupted as claimed. It was recognized that no commission could expect to examine even a small proportion of the population of a country in order to confirm that none had smallpox. Moreover, if experts of the right calibre were to participate, it was appreciated that they would be unable to spend more than 3–4 weeks away from their normal place of work. The objective of an international commission was to assess the quality of the local surveillance programme and to determine whether cases of smallpox would have been detected if transmission had occurred during the preceding 2 years. In doing so, commission members themselves usually carried out their own, rather limited surveys.

In most instances preliminary visits by one or two of the commission's members (often

Plate 24.8. Holger B. Lundbeck (b. 1924), Director of the National Bacteriological Laboratory, Stockholm, participated in several international commissions for the certification of smallpox eradication and was an influential member of the Global Commission. He is shown here signing the scroll certifying eradication which is reproduced as the frontispiece of this book.

the chairman) were arranged by WHO so that they could examine the state of the documentation and recommend any additional measures which they thought were indicated.

After arrival in the country to be certified, the commission usually spent 2–3 days in the capital reviewing the country report. If several countries were involved, the commission selected a conveniently situated capital city for its initial meeting, during which it scrutinized all the country reports; it then divided up into several groups to visit individual countries, and finally reassembled to assess the findings and prepare a report. In each country, in order to visit as many areas as possible, the commissions usually divided themselves up into teams consisting of one or two members, the areas selected being those identified as having the least satisfactory documentation or as being at unusual risk. Members of the commission had both the right and the responsibility to decide exactly which areas, villages and health units they would visit each day. The teams travelled extensively in the field for 1–3 weeks before reconvening.

PROCEDURES FOR GLOBAL CERTIFICATION

By June 1977, international commissions had already visited or were preparing to visit all the previously endemic countries and countries at special risk. However, there were other countries in which there was a need to determine what measures should be taken in order to certify that the transmission of smallpox had been interrupted for at least 2 years. Furthermore, there were several countries—China, Democratic Kampuchea, Iran, Iraq, Madagascar, Namibia, South Africa, Southern Rhodesia (Zimbabwe), the Syrian Arab Republic, Thailand and Viet Nam—for which the staff of the Smallpox Eradication unit needed outside advice on how best to deal with the situation. Clearly, countries such as Madagascar and Thailand would not be expected to undertake the same kind of precertification activities as had been carried out in the countries of western Africa, yet they could not be ignored. Others, such as Democratic Kampuchea, Namibia, South Africa and Southern Rhodesia (Zimbabwe), were not readily accessible to WHO staff.

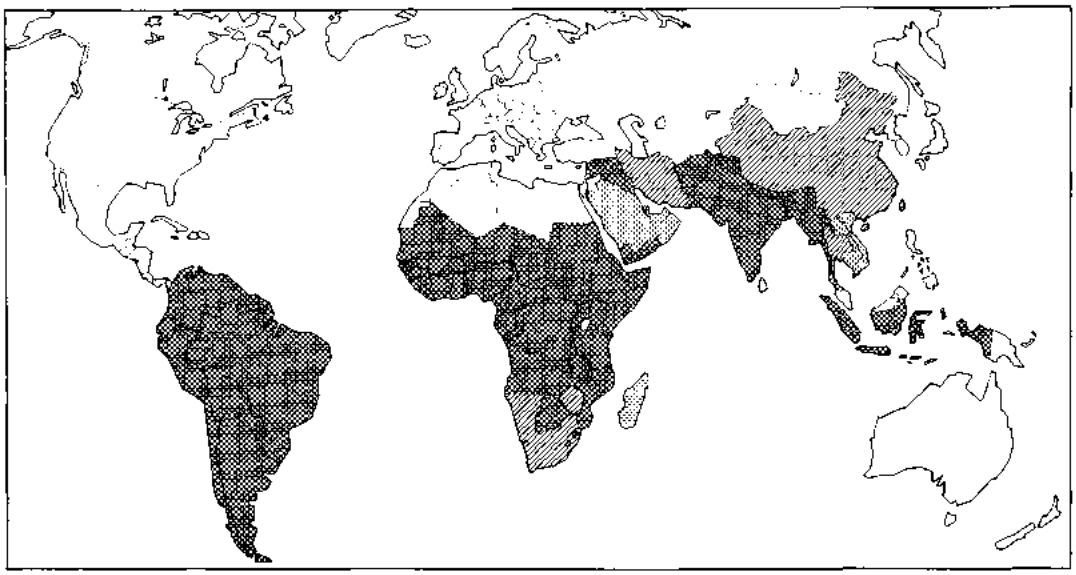
Another important matter was the international credibility of a claim that smallpox had been eradicated throughout the world. The problem was that, if the staff of the Smallpox Eradication unit themselves were to decide as to the data to be provided in confirmation of eradication, such a decision was open to criticism by government officials and health professionals around the world, since those responsible for a programme obviously have a stake in its success. However objective their judgements might be, other scientists would be justified in questioning that objectivity.

As has already been pointed out, the practical implications of the global eradication of smallpox were substantial. If the World Health Assembly were to accept that smallpox had been eradicated, this would mean that all preventive measures against the disease, including routine vaccination and international certificates of smallpox vaccination, could be abandoned. However, it was clear that these changes in well-established public health practices and the consequent financial savings would materialize only if the international community confidently accepted the assertion that smallpox had indeed been eradicated, first from countries, regions and continents and, finally, from the world. To gain such acceptance would not be a simple matter, for disbelief in the feasibility of smallpox eradication was common throughout the duration of the Intensified Smallpox Eradication Programme.

Consultation on the Worldwide Certification of Smallpox Eradication

The practical solution to the problems described above was to set up a global commission of respected scientists which, as one of its functions, could advise WHO as to what data should be collected, for clearly this was a matter of judgement. Eventually, when such outside experts were fully satisfied that global eradication had been achieved, this conclusion would have been reached, not by WHO itself or by putting together the reports of a series of international commissions each dealing with one or a few countries, but by an international group of senior scientists and administrators capable of taking a global view of the problem.

To obtain advice on how best to achieve the certification of global eradication, the Director-General of WHO convened a consultation which was held in Geneva on 11–13



Category 1 – **Formal certification by international commissions** of experts visiting the countries concerned and assessing their smallpox-free status by examining records and making field visits to determine whether surveillance activities would have been adequate to detect a case of smallpox if one had occurred during the previous 2 years.

Category 2 – **Certification by the visit of selected experts** to verify and document the smallpox incidence since 1960, the last known outbreak and control measures employed, and procedures for handling suspected cases.

Category 3 – **Certification through submission of detailed country reports.**

Category 4 – **Official statements by countries** declaring their smallpox-free status during the previous 2 years and signed by government health authorities.

Fig. 24.2. Methodologies used for the certification of smallpox eradication in various categories of countries.

October 1977. The participants (Annex 24.2) included 17 experts on epidemiology, virology and public health administration from 15 countries: 3 from Africa, 3 from the Americas, 4 from Asia, 6 from Europe and 1 from Oceania. During the succeeding 2 years, most of the participants in the consultation served on the Global Commission for the Certification of Smallpox Eradication. Documentation for the meeting had been prepared by the staff of the Smallpox Eradication unit, and the consultation made important recommendations (WHO/SE/77.98) as to how certification should proceed so that the stage could be reached, as quickly as possible, at which it could be certified that smallpox had been eradicated globally. For this purpose, the countries of the world were divided into three categories; a fourth was subsequently added by the Global Commission (Fig. 24.2). The various categories are discussed below.

Category 1—Formal certification by international commissions

The most stringent assessment was required in countries in which smallpox was endemic at the inception of the Intensified Smallpox Eradication Programme in 1967, or had become endemic since then. For such countries, the consultation recommended that the established procedure of formal certification by designated international commissions should be carried out. In October 1977, when the consultation met, this formal certification had already been performed in South America (1973), Indonesia (1974), 15 countries in western Africa (1976),

Afghanistan and Pakistan (1976), 5 countries in south-eastern Asia (1977) and 9 countries in central Africa (1977) (see Plate 24.11). The additional countries scheduled for formal certification from November 1977 onwards were:

South-eastern Asia: Bangladesh and Burma (scheduled for November–December 1977).

South-eastern Africa: Malawi, Mozambique, the United Republic of Tanzania and Zambia (scheduled for March 1978).

Eastern-central Africa: Sudan and Uganda.

Southern Africa, group I: Angola, Botswana, Lesotho and Swaziland.

Southern Africa, group II: Namibia, South Africa and Southern Rhodesia (Zimbabwe). Because of political complexities (see Chapter 26) it was apparent by 1978 that it would be both difficult and time-consuming to organize the certification of these countries by international commissions. Instead they were investigated as set out for Category 2 countries (see below) and certified by the Global Commission.

The Horn of Africa and neighbouring countries: Democratic Yemen, Djibouti, Ethiopia, Kenya, Somalia and Yemen.

Category 2 — Certification by the visit of selected experts

The consultation considered that some countries in which smallpox was not endemic in 1967 required special consideration, short of a visit by an international commission, because of the inadequacy of surveillance and/or their proximity to areas in which smallpox had recently been endemic. For such countries, it was suggested that visits by international experts (subsequently Global Commission members or WHO consultants) and/or WHO epidemiologists should be arranged during 1978 in order to verify and document their smallpox eradication status. The countries in this category are discussed below.

China. Although it was widely believed that smallpox transmission had been interrupted in China in about 1960, the country did not become a member of WHO until 1972. Even as late as 1977, little information was available to WHO as to what had been achieved, or how, or when, except that smallpox had been eradicated in China in 1960 or thereabouts. Since it was the most populous country on earth, and one in which smallpox had been widespread for over 1800 years, the consultation believed that special investigations were needed to assure the international community that smallpox was no longer endemic there.

Iran, Iraq and the Syrian Arab Republic. Although endemic smallpox had been eliminated from these countries in 1963, 1959 and 1957 respectively, variola major had become established again in all of them between 1970 and 1972. Smallpox was first reintroduced into Iran from Afghanistan and subsequently spread into Iraq and the Syrian Arab Republic (see Chapter 23). Because of the extent and duration of the outbreak, the consultation suggested that each of these countries should be asked to submit a detailed report of its surveillance programme and smallpox eradication activities during at least the past 5 years, after which members of the consultation or its successor, the Global Commission, would visit each country to review the situation.

Thailand. Although smallpox had ceased to be endemic in Thailand in 1962, the good communications with Bangladesh and India indicated the need for special evaluation, particularly in the border area of Thailand, Burma and the Lao People's Democratic Republic, which was notoriously inaccessible.

Category 3—Certification through submission of detailed country reports

WHO was requested by the consultation to ask certain countries to provide detailed reports, including but not limited to data on the incidence of smallpox since 1960, an account of the last known outbreak and the control measures employed, and the method of approach to be adopted should a suspected case of smallpox be found. Several countries about which detailed information was not available to the Global Commission fell into this category and are discussed below.

Gulf States: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and the United Arab Emirates. These countries had been free of endemic smallpox since 1963 but had experienced sporadic importations up to 1971. The Secretariat-General for the Ministers of Health of the Arab States of the Gulf was asked to coordinate the preparation of special country reports from these States.

South-east Asian countries. Because fighting had been going on for so long, detailed information was lacking from Democratic Kampuchea, the Lao People's Democratic Republic and Viet Nam. A special report was

also requested from China (Province of Taiwan).

Madagascar. Although the last reported case of smallpox in Madagascar occurred in 1934, rumours had reached the consultation of outbreaks of a disease that might have been smallpox. A special report was therefore requested.

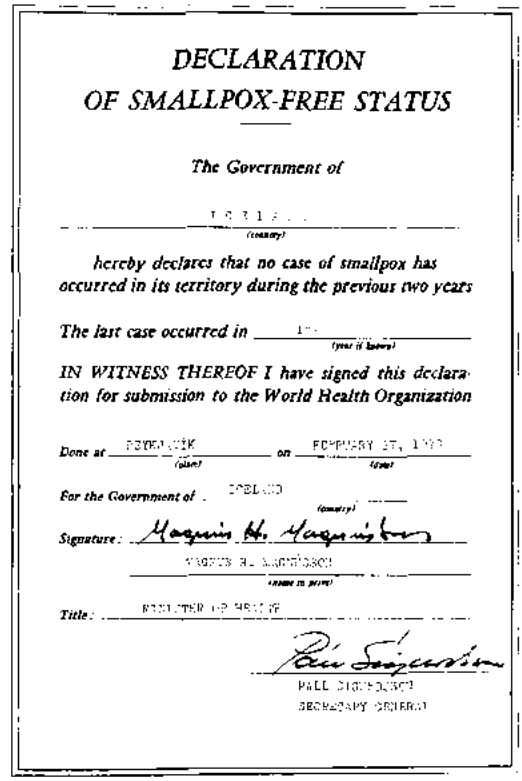
Category 4—Official statements by countries

In addition to these more stringent requirements, it was decided that every country and area should provide WHO with a signed statement that smallpox had not been present in that country or area during at least the preceding 2 years. Certification of freedom from smallpox by an international commission was considered to constitute such a statement.

Establishment and Responsibilities of the Global Commission

Finally, the consultation recommended that, since smallpox eradication was an unprecedented achievement, it should be promptly certified and appropriately recognized. For that reason, "... To assist in this effort and to provide authoritative endorsement, a formally constituted International Commission for the Global Certification of Smallpox Eradication (Global Commission) should be established by WHO to provide consultative assistance and verification of this event" (WHO/SE/77.98). Early in 1978 most of the participants in the consultation were designated by the Director-General of WHO as constituting the Global Commission for the Certification of Smallpox Eradication and at the same time a few new members were introduced (Annex 24.2; Plate 24.10).

Fenner, who had been Chairman of the consultation, was elected Chairman of the Global Commission, and acted in this capacity at the meetings in 1978 and 1979 (see below). Dr W. Koinange of Kenya was the Vice-Chairman at the 1977 consultation and Dr Jan Kostrzewski of Poland was Vice-Chairman at both meetings of the Global Commission. Arita, as Chief of the Smallpox Eradication unit, served as secretary both of the consultation and of the Global Commission. As has already been mentioned, Global Commission members were included in almost all of the 11 international commissions which met in 1978



DECLARATION
OF SMALLPOX-FREE STATUS

The Government of

ICELAND
(country)

hereby declares that no case of smallpox has occurred in its territory during the previous two years

The last case occurred in 1...
(year if known)

IN WITNESS THEREOF I have signed this declaration for submission to the World Health Organization

Done at REYKJAVIK (place) *on* FEBRUARY 27, 1...
(date)

For the Government of ICELAND (country)

Signature: Magnús H. Magnússon

MAGNÚS H. MAGNÚSSON
(name in print)

Title: REGISTER OF BIRTHS

Páll Sigurðsson

PÁLL SIGURÐSSON
SECRETARY GENERAL

Plate 24.9. Official statements, like this one from Iceland, were received from 121 countries and territories declaring they had not had a case of smallpox for at least 2 years. They were accepted by the Global Commission for all countries other than the 79 where special measures were deemed necessary.

and 1979 to deal with specific geographical areas, an experience which further strengthened the assessment by the Global Commission of the progress of eradication as a whole.

The Global Commission met in Geneva in December 1978 and again in December 1979 to review certification activities in various countries in the four categories defined by the consultation and to consider other issues relevant to global certification. At the 1979 meeting, the Global Commission debated and approved its final report (World Health Organization, 1980), which was submitted to the Thirty-third World Health Assembly.

CHRONOLOGY OF CERTIFICATION

As has previously been noted, special measures had to be taken in 79 countries before the declaration of global smallpox eradication could be made. Between 1973 and 1979,

L. BIANCO

Plate 24.10. Participants at the meeting of the Global Commission for the Certification of Smallpox Eradication, 6–9 December 1979. *Left to right, front row:* Yemane Tekeste (Ethiopia), Z. Ježek (WHO), I. D. Ladnyi (WHO), I. Arita (WHO), Z. Islam (WHO), S. E. Woolnough (WHO), C. I. Sands (WHO); *second row:* **S. S. Marennikova (USSR), J. Azurin (Philippines), P. N. Burgasov (USSR), F. Fenner (Australia), J. Kostrzewski (Poland), D. A. Henderson (USA), W. Koinange (Kenya)**, Jiang Yutu (China); *third row:* A. I. Gromyko (WHO), **R. N. Basu (India), J. M. Aashi (Saudi Arabia), B. A. Rodrigues (Brazil), R. Netter (France), J. S. Moeti (Botswana), Kalisa Ruti (Zaire), P. N. Shrestha (Nepal)**, B. C. Dazo (WHO), M. C. de Souza (WHO), **Zhang Yihao (China)**, J. Magee (WHO); *back row:* G. Meiklejohn (USA), **P. F. Wehrle (USA)**, J. G. Breman (USA), **H. B. Lundbeck (Sweden), K. R. Dumbell (United Kingdom), I. Tagaya (Japan), A. Deria (Somalia)**, J. L. Tulloch (WHO), R. N. Evans (WHO), J. F. Wickett (WHO). The names of the Commission members are in bold type.

therefore, the status of smallpox in these countries was assessed by WHO and by independent groups convened by the WHO Secretariat (Fig. 24.3). The eradication of smallpox in 63 of these countries was certified by international commissions; the situation in the other 16 (No. 53–64, 66–67 and 78–79) was evaluated by other means.

Of the 79 countries concerned, 31 had been certified by international commissions between 1973 and 1976 (see Plate 24.11), but from 1977 onwards certification activities were much accelerated in view of the fact that global eradication was imminent. The 1977 Consultation on the Worldwide Certification of Smallpox Eradication and the establishment of a Global Commission substantially promoted the prompt completion of these activities, since these bodies were a source of advice and recommendations.

In May 1978, when 49 of the 79 countries had already been certified, a document entitled *Methodology for Preparation of Appropriate Data for the [30] Countries Remaining to be Certified Free of Smallpox* (SME/78.6) was prepared by the staff of the Smallpox Eradication unit. On the basis of experience gained with previous certifications, the document set out the minimum requirements for the country reports, guidelines and standard forms for field activities such as pockmark surveys and chickenpox surveillance, and procedures for the collection and dispatch of laboratory specimens. It was distributed to all countries still to be certified and proved to be extremely useful for both health planners and field workers in their preparations for certification.

Despite the existence of many politically insecure areas in the late 1970s and the large

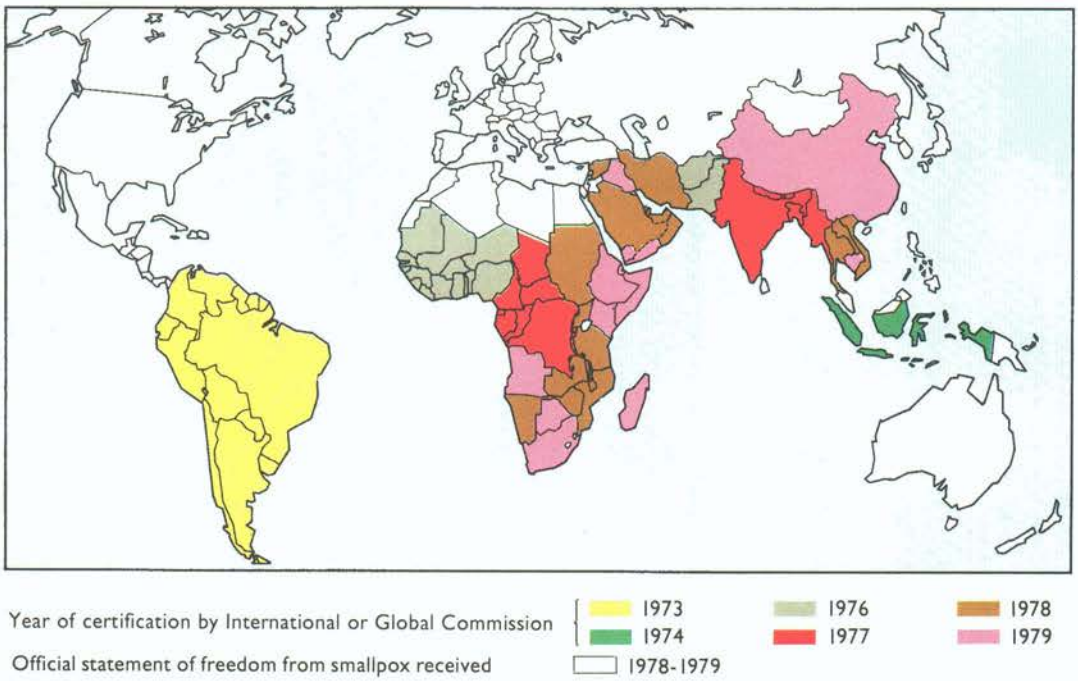


Plate 24.11. Chronological progress of certification in the 79 countries where special measures were necessary. All other countries provided an official statement that smallpox had not occurred in their country during the preceding 2 years.

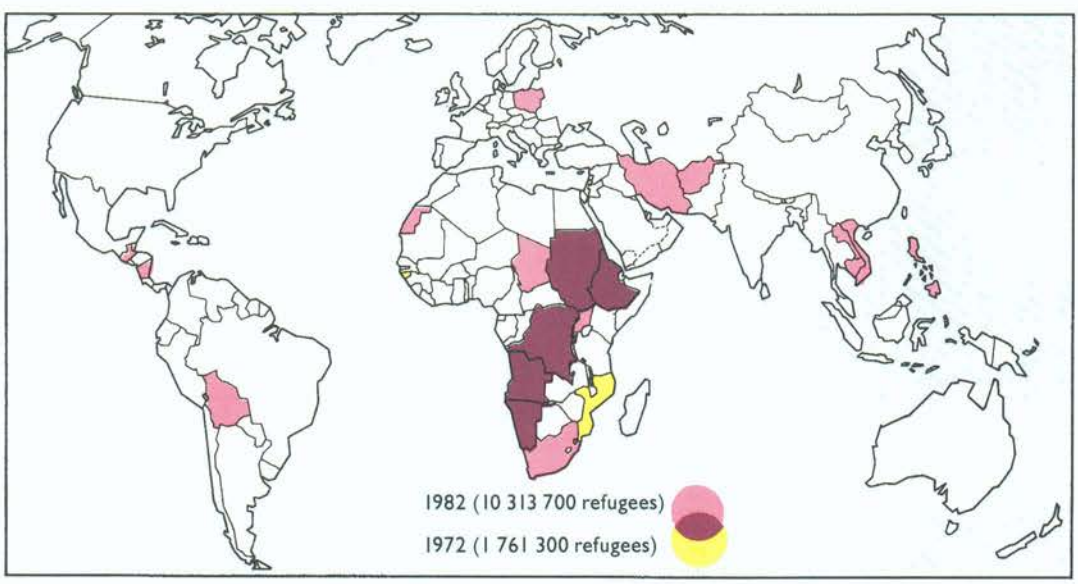


Plate 24.12. Smallpox eradication, and its certification between 1973 and 1979, were conducted when the numbers of refugees in the world were growing constantly. This map shows the country of origin of refugees assisted by the Office of the United Nations High Commissioner for Refugees in 1972 and in 1982 (the purple shading indicates countries common to both years). Although it clearly depicts the magnitude of this distressing problem, it does not show some areas in which, before or between those years, the conditions that caused people to become refugees also made eradication work particularly difficult — e.g., Nigeria (1967–1968), Bangladesh (1970–1971), and the Horn of Africa (1974–1978).

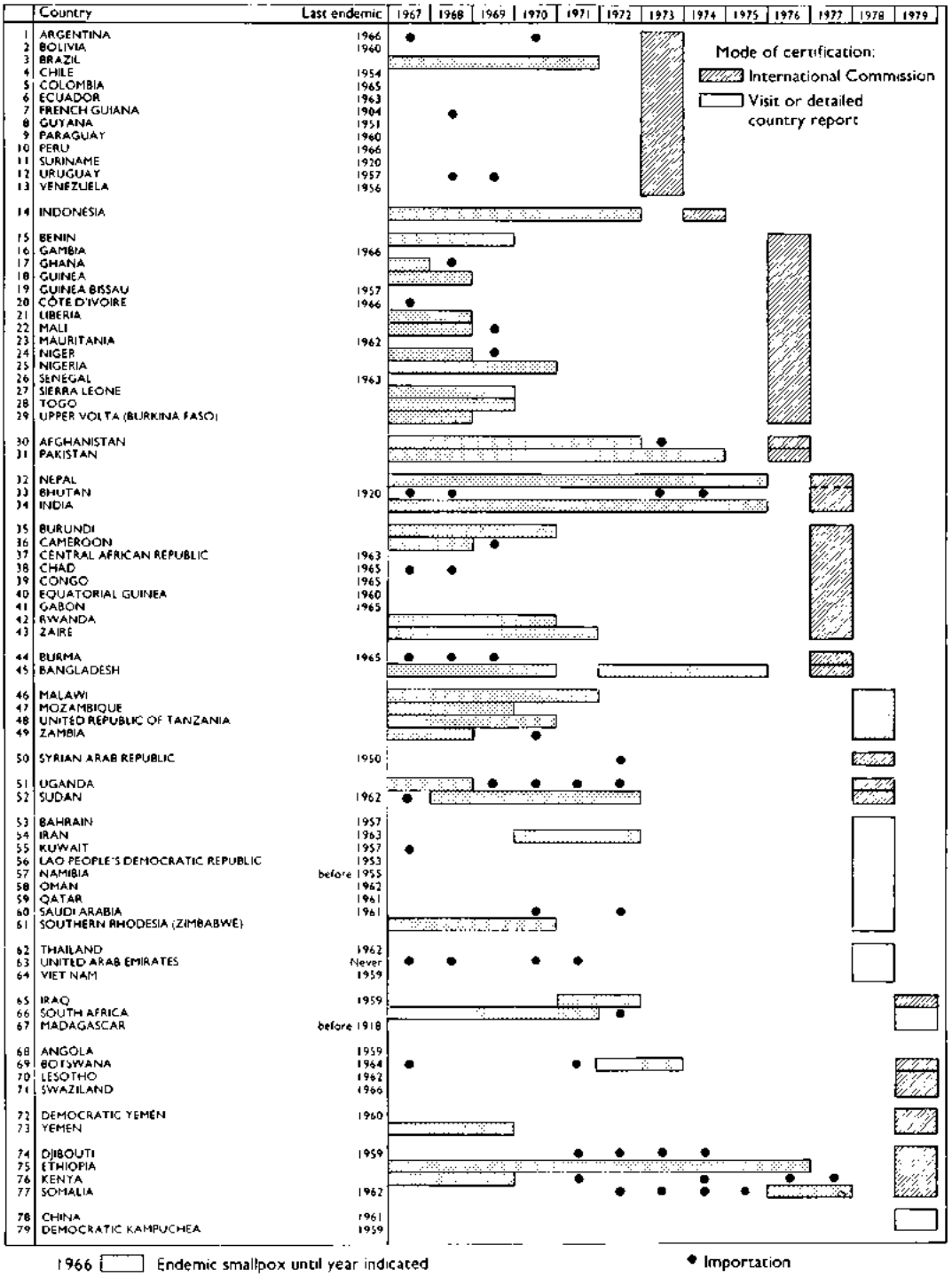


Fig. 24.3. Countries requiring special procedures for the certification of smallpox eradication. The year when the country ceased to be endemic, the year of the last known case, and the year and method of certification are also shown.

number of refugees, of whom there were ten times more in 1982 than in 1972 (see Plate 24.12), certification activities, including field visits by outside experts where necessary, proceeded surprisingly well, perhaps owing to the interest of the international community in this unprecedented event in the history of medicine.

Certification activities were strongly supported by a vigorous information campaign. From March 1978 to August 1980 a special information officer, Mr James Magee, was recruited to ensure good communications with major media agencies as well as medical periodicals. The goal of the information campaign was to reach beyond the scientific community with the news that:

(1) the world's last naturally occurring case of endemic smallpox had been found in Somalia on 26 October 1977;
(2) this was being confirmed globally by certification procedures involving an intensive search for cases; and
(3) it was expected that, if all went well, the target date for the declaration of global eradication, 26 October 1979—i.e., 2 years after the case in Somalia—would be met.

The benefits of eradication to the international community were stressed, including the end of the misery caused by this disease throughout human history and the enormous financial savings to the public health sector with the universal discontinuation of smallpox vaccination and associated control measures. Those with doubts were encouraged to speak out well in advance of the final global certification and countries were urged to change their legislation on smallpox vaccination at an early date.

The last certification activities by international commissions took place in October 1979 in the Horn of Africa—Djibouti, Ethiopia, Kenya, and Somalia, where, as has just been mentioned, the world's last case of endemic smallpox was discovered in October 1977. The 4 commissions that visited the countries of the Horn of Africa in October 1979 subsequently met in combined session in Nairobi, where they considered the region as a whole. On 26 October 1979, exactly 2 years after the onset of rash in the last case of endemic smallpox in the world, smallpox eradication was certified for Africa at a ceremony in which the Director-General of WHO and the directors of the Regional Offices for Africa and the Eastern Mediterranean participated.

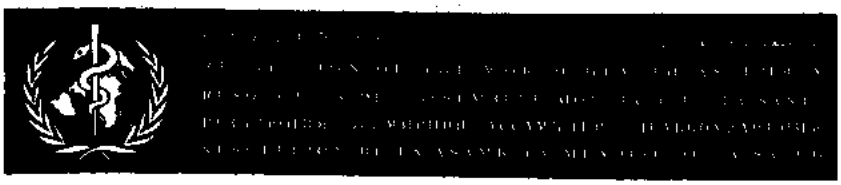
Plate 24.13. Gordon Meiklejohn (b. 1911), Professor of Medicine at the University of Colorado, Denver, USA. Worked with Dr A. R. Rao in Madras in the early 1960s and served as a WHO consultant on smallpox almost every year from the mid-1960s, and for a full year in 1968–1969. He was a member of several international commissions for the certification of smallpox eradication and was responsible for the preparation of the first draft of the Final Report of the Global Commission.

Certification of the Horn of Africa left only 2 countries uncertified, China and Democratic Kampuchea. However, in November 1979, a report prepared after the visit of a WHO team to China became available and the smallpox situation in Democratic Kampuchea was clarified. On 9 December 1979, at its last meeting in Geneva, the Global Commission agreed to certify smallpox eradication in these 2 countries.

By the end of 1979 all other countries—i.e., excluding those visited by the international commissions or certified by the Global Commission on the basis of other evidence—had submitted to WHO their signed declarations that no cases of smallpox had occurred during at least 2 years. The requirements for global certification recommended by the 1977 Consultation on the Worldwide Certification of Smallpox Eradication had thus been met.

DECLARATION OF THE GLOBAL ERADICATION OF SMALLPOX

The ultimate responsibility of the Global Commission, once it was satisfied that world-



The Thirty-third World Health Assembly, on this the 8th day of May 1980;

Having considered the developments and results of the global programme on smallpox eradication initiated by WHO in 1958 and intensified since 1967;

1. DECLARES SOLEMNLY THAT THE WORLD AND ALL ITS PEOPLES HAVE WON FREEDOM FROM SMALLPOX, WHICH WAS A MOST DEVASTATING DISEASE SWEEPING IN EPIDEMIC FORM THROUGH MANY COUNTRIES SINCE EARLIEST TIME, LEAVING DEATH, BLINDNESS AND DISFIGUREMENT IN ITS WAKE AND WHICH ONLY A DECADE AGO WAS RAMPANT IN AFRICA, ASIA AND SOUTH AMERICA;

2. EXPRESSES ITS DEEP GRATITUDE TO ALL NATIONS AND INDIVIDUALS WHO CONTRIBUTED TO THE SUCCESS OF THIS NOBLE AND HISTORIC ENDEAVOUR;

3. CALLS THIS UNPRECEDENTED ACHIEVEMENT IN THE HISTORY OF PUBLIC HEALTH TO THE ATTENTION OF ALL NATIONS, WHICH BY THEIR COLLECTIVE ACTION HAVE FREED MANKIND OF THIS ANCIENT SCOURGE AND, IN SO DOING, HAVE DEMONSTRATED HOW NATIONS WORKING TOGETHER IN A COMMON CAUSE MAY FURTHER HUMAN PROGRESS.

Plate 24.14. Resolution WHA33.3, the formal declaration of the eradication of smallpox, based on the report of the Global Commission to the Director-General of WHO, was adopted unanimously by the Thirty-third World Health Assembly on 8 May 1980.

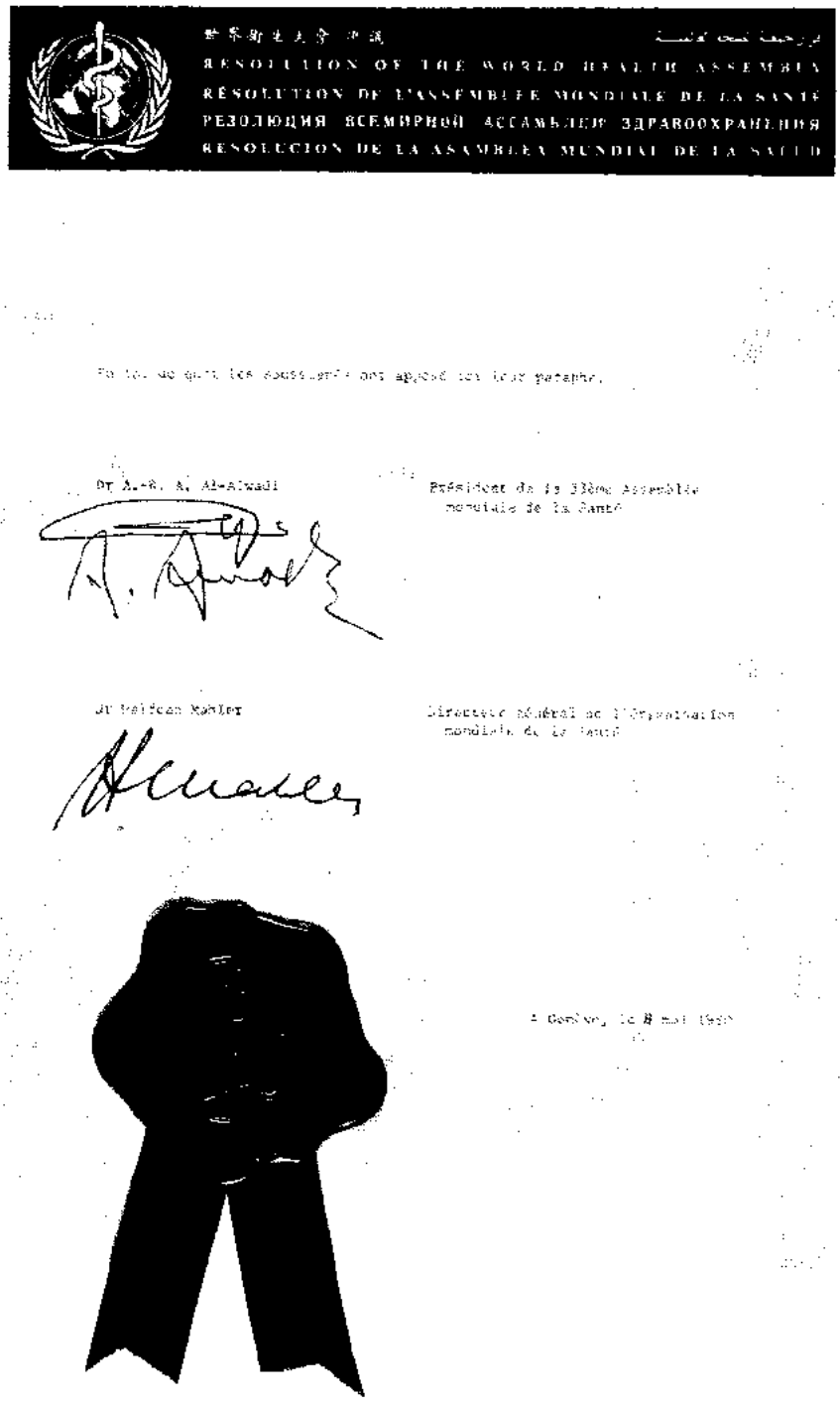

RESOLUTION OF THE WORLD HEALTH ASSEMBLY
RÉSOLUTION DE L'ASSEMBLÉE MONDIALE DE LA SANTÉ
РЕЗОЛЮЦИЯ ВСЕМИРНОЙ АССАМБЛЕИ ЗДРАВООХРАНЕНИЯ
RESOLUCION DE LA ASAMBLEA MUNDIAL DE LA SALUD
Dr A.-R. A. Al-Awadi
Président de la 33ème Assemblée mondiale de la Santé
Dr Halfdan Mahler
Directeur général de l'Organisation mondiale de la Santé

Plate 24.15. As the President of the Thirty-third World Health Assembly, Dr A-R. A. Al-Awadi, and the Director-General of WHO, Dr Halfdan Mahler, signed resolution WHA33.3, the President remarked: "While doctors sign the death certificates of people, today we are signing the death certificate of a disease".

Plate 24.16. The ceremony of the declaration of global eradication of smallpox, on 8 May 1980, during the eighth plenary meeting of the Thirty-third World Health Assembly. **A:** Dr Frank Fenner (inset), Chairman of the Global Commission, addressed the Assembly and handed to the President the scroll that had been signed by the members of the Commission (see frontispiece). **B:** The President of the Assembly, Dr A-R. A. Al-Awadi, signing resolution WHA33.3, with the Director-General of WHO, Dr Halfdan Mahler, looking on.

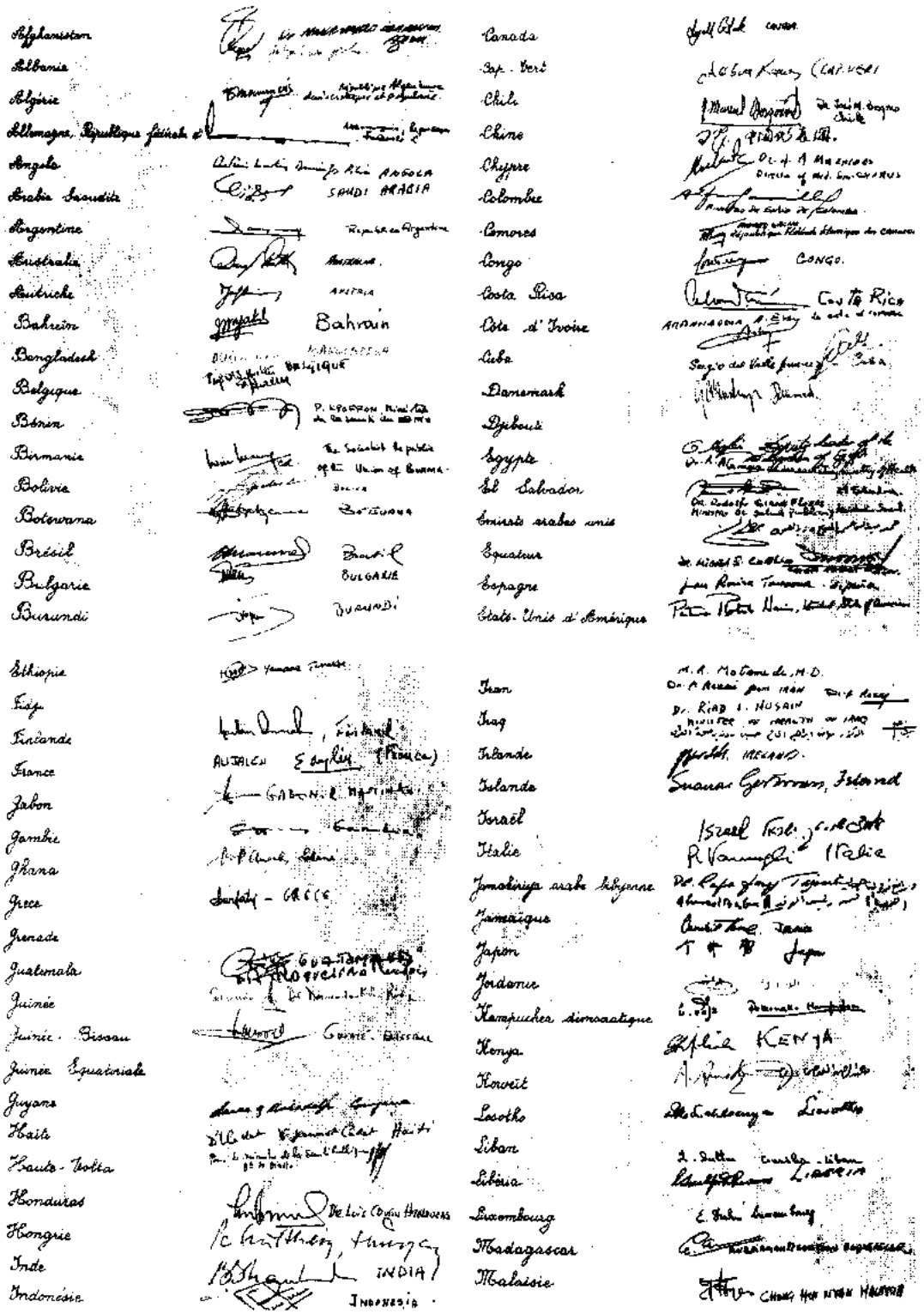


Plate 24.17. Signatures of the delegates of Member States, from Afghanistan to Malaysia, appended to resolution WHA33.3.

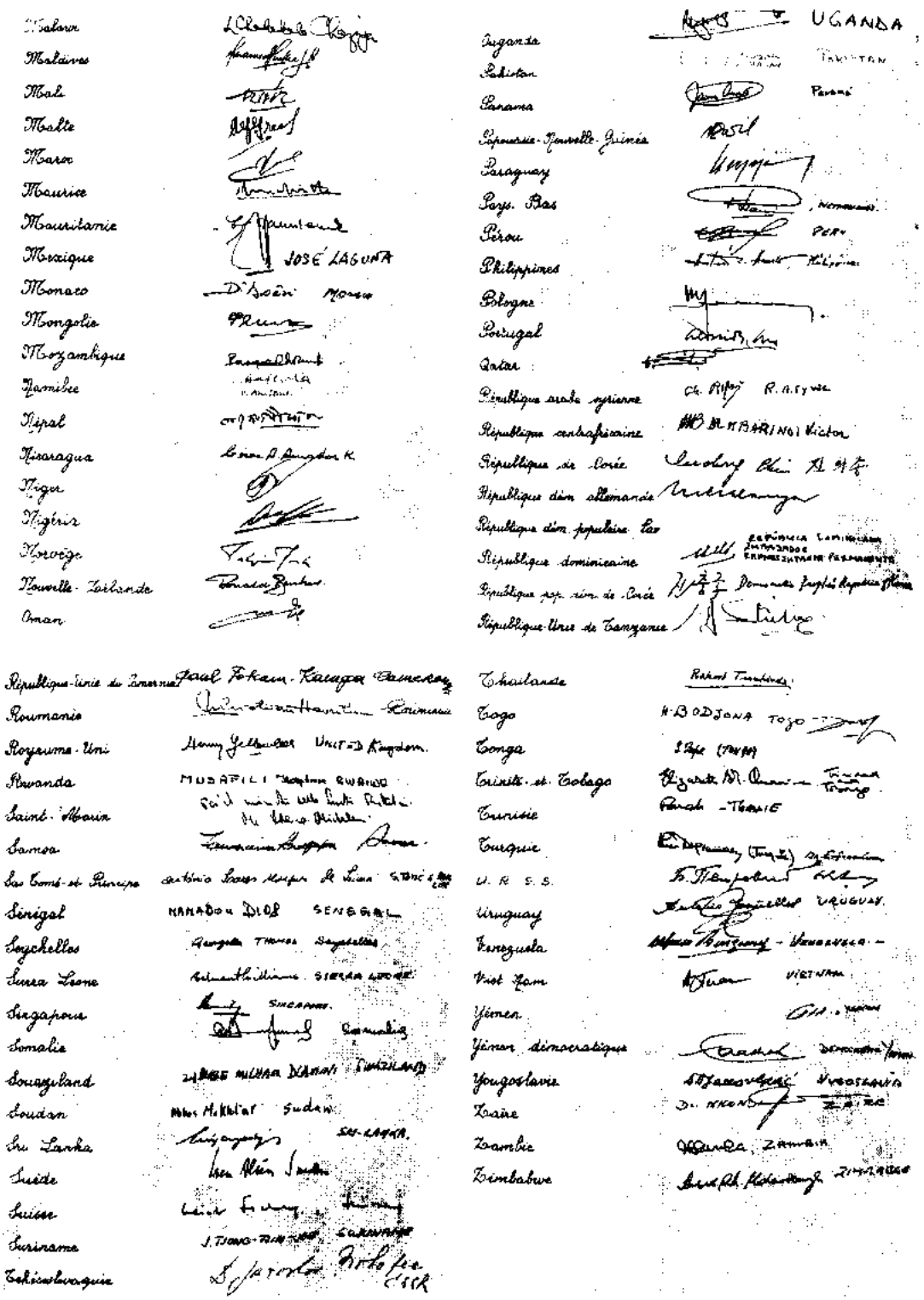


Plate 24.18. Signatures of the delegates of Member States, from Malawi to Zimbabwe, appended to resolution WHA33.3.

wide eradication of smallpox had been achieved, was to document the reasons for its decision in a way that would allow the World Health Assembly to declare that smallpox had been eradicated. In addition, it was important that a post-eradication strategy should be planned and machinery developed to implement it.

During 1979, with the help of Dr Gordon Meiklejohn, a WHO consultant, the Smallpox Eradication unit drafted a report for consideration by the Global Commission. This was reviewed in detail by the 12 members of the Global Commission present in Nairobi in October 1979 (see Chapter 27), and the revised report was the main subject of discussion at the 4-day final meeting of the Global Commission in December 1979. The final report (World Health Organization, 1980) outlines the criteria on the basis of which all members of the Global Commission signed a document proclaiming the global eradication of smallpox (see frontispiece). It also contained 19 recommendations covering all aspects of a post-eradication strategy (see Chapter 28) designed to ensure that all the countries of the world could remain confident that smallpox had indeed been eradicated.

On 8 May 1980 the Thirty-third World Health Assembly reviewed the Global Commission's report and declared that smallpox had been eradicated throughout the world. There were two resolutions: resolution WHA33.3 (see Plates 24.14–24.16) declared that the global eradication of smallpox had been achieved and resolution WHA33.4 endorsed the Global Commission's recommendations on policy for the post-eradication era (see Chapter 28).

ANNEX 24.1. MEMBERSHIP OF INTERNATIONAL COMMISSIONS FOR THE CERTIFICATION OF SMALLPOX ERADICATION

The positions held by members at the time of the international commissions give some indication of their standing and expertise. Members of the Global Commission who were also members of international commissions both before and after the establishment of the Global Commission are indicated by the letters GC in parentheses after their names.

1. SOUTH AMERICA: 12–25 August 1973 (PAHO document CD22/19)

Dr A. N. Bica	Secretary of Public Health, Ministry of Health, Rio de Janeiro, Brazil (*Chairman*)
Dr F. J. C. Cambournac	Director, Institute of Hygiene and Tropical Medicine, Lisbon, Portugal
Dr E. Echezuría	Chief, Department of Demography and Epidemiology, Ministry of Health, Caracas, Venezuela (*Rapporteur*)
Dr J. D. Millar	Director, State and Community Services Division, Center for Disease Control, Atlanta, GA, USA
Dr R. J. Wilson	Chairman, Connaught Medical Research Laboratories Ltd, University of Toronto, Canada

2. INDONESIA: 15–25 April 1974 (WHO/SE/74.68)

Dr N. McK. Bennett	Specialist Physician and Deputy Superintendent, Fairfield Hospital, Melbourne, Australia
Dr J. J. Dizon	Chief of Disease Intelligence, Disease Intelligence Centre, Department of Health, Manila, Philippines
Dr J. S. Gill	Assistant Director, Health and Epidemiology, Ministry of Health, Kuala Lumpur, Malaysia (*Rapporteur*)
Dr S. Kumarapathy	Senior Registrar, Quarantine and Epidemiology, Environmental Public Health Division, Ministry of Environment, Singapore

Dr J. Sulianti Saroso	Director-General for the Control and Prevention of Communicable Diseases, Ministry of Health, Jakarta, Indonesia
Dr I. Tagaya (GC)	Director, Department of Enteroviruses, National Institute of Health, Tokyo, Japan
Dr P. F. Wehrle (GC)	Hastings Professor of Pediatrics, Los Angeles County—University of Southern California Medical Center, Los Angeles, CA, USA (*Chairman*)

3. WESTERN AFRICA: 23 March–15 April 1976 (AFR/Smallpox/80)
Countries included: Benin, Côte d'Ivoire, Gambia, Ghana, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone, Togo and Upper Volta (Burkina Faso).

Dr S. Bédaya-Ngaro	Inspector General of Health Services, Bangui, Central African Republic
Dr W. Koinange (GC)	Director, Division of Communicable Disease Control, Ministry of Health, Nairobi, Kenya (*Chairman*, Abidjan)
Dr I. D. Ladnyi	Chief, Central Board of Quarantinable Diseases, Ministry of Health, Moscow, USSR
Dr Lekie Botee	Director-General, Department of Public Health, Kinshasa, Zaire (*Chairman*, Brazzaville)
Dr R. Netter (GC)	Director-General, National Health Laboratory, Paris, France
Dr M. I. D. Sharma	Director (retired), National Institute of Communicable Diseases, New Delhi, India
Dr P. F. Wehrle (GC)	Hastings Professor of Pediatrics, Los Angeles County—University of Southern California Medical Center, Los Angeles, CA, USA (*Rapporteur*)

4. AFGHANISTAN: 22–29 November 1976 (WHO/SE/77.89)
and
5. PAKISTAN: 6–18 December 1976 (WHO/SE/77.90)

Dr H. S. Bedson	Professor of Medical Microbiology, University of Birmingham, Medical School, Birmingham, England
Dr N. McK. Bennett	Specialist Physician and Deputy Superintendent, Fairfield Hospital, Melbourne, Australia
Dr A. I. Idris	Director-General, Epidemiology, Ministry of Health, Khartoum, Sudan (*Chairman*, Pakistan)
Dr G. Meiklejohn	Professor of Medicine, University of Colorado Medical Center, Denver, CO, USA (*Rapporteur*, Afghanistan and Pakistan)
Dr N. Kumara Rai	Director, Planning Department, Directorate General for Communicable Disease Control, Ministry of Health, Jakarta, Indonesia
Dr P. N. Shrestha (GC)	Chief, Smallpox Eradication Project, Department of Health Services, Kathmandu, Nepal (*Chairman*, Afghanistan)

6. CENTRAL AFRICA: 6–30 June 1977 (AFR/Smallpox/86)
Countries included: Burundi, Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Rwanda and Zaire.

Dr P. Agbodjan	Chief, Major Endemic Diseases Service, General Directorate for Health, Lomé, Togo
Dr J. G. Breman	Epidemic Intelligence Officer (Michigan Department of Public Health), Bureau of Epidemiology, Center for Disease Control, Atlanta, GA, USA

Dr E. Coffi	Director, Institute of Hygiene, Ministry of Public Health, Abidjan, Côte d'Ivoire
Dr F. Dekking	Health Science Laboratory, University of Amsterdam, Netherlands
Dr A. K. M'Baye	Chief Medical Officer, Major Endemic Diseases Service, and Deputy Director of Public Health, Dakar, Senegal (*Chairman*)
Dr R. Netter (GC)	Director-General, National Health Laboratory, Paris, France (*Rapporteur*)
Dr M. Yekpe	Chief, Communicable Diseases Service, Ministry of Public Health, Cotonou, Benin

7. INDIA: 4–23 April 1977 (SEA/Smallpox/78)
NEPAL: 4–13 April 1977 (SEA/Smallpox/80)
BHUTAN: 28 March–1 April 1977; 22 April 1977 (SEA/Smallpox/80)

India and Bhutan

Dr J. Červenka	Chief (Epidemiology), Institute of Epidemiology and Microbiology, Bratislava, Czechoslovakia
Dr W. A. B. de Silva	Deputy Director (Planning), Ministry of Health, Colombo, Sri Lanka
Dr F. Fenner (GC)	Director, Centre for Resource and Environmental Studies, The Australian National University, Canberra, Australia (*Rapporteur*)
Dr H. Flamm	Institute of Hygiene, University of Vienna, Austria
Lt.-Gen. R. S. Hoon	Director-General, Armed Forces Medical Services, New Delhi, India
Dr T. Kitamura	Chief, Division of Poxviruses, National Institute of Health, Tokyo, Japan
Dr W. Koinange (GC)	Director, Division of Communicable Disease Control, Ministry of Health, Nairobi, Kenya
Dr J. Kostrzewski (GC)	Secretary, Medical Section, Polish Academy of Sciences, Warsaw, Poland (*Chairman*)
Dr H. B. Lundbeck (GC)	Director, National Bacteriological Laboratory, Stockholm, Sweden
Dr A. M. Mustaqul Huq	Director of Health Services (Preventive), Ministry of Health, Dhaka, Bangladesh
Dr D. M. Mackay	Ross Institute of Tropical Hygiene, London School of Hygiene and Tropical Medicine, London, England
Dr M. F. Polak	Scientific Officer, Faculty of Medicine, Catholic University, Nijmegen, Netherlands
Dr R. Roashan	President, Foreign Relations Department, Ministry of Public Health, Kabul, Afghanistan
Dr D. J. Sencer	Director, Center for Disease Control, Atlanta, GA, USA
Dr U Thein Nyunt	Director, Disease Control, Ministry of Health, Rangoon, Burma
Dr V. M. Zhdanov	Director, Institute of Virology, Academy of Medical Sciences, Moscow, USSR

Nepal

Dr T. Kitamura	Chief, Division of Poxviruses, National Institute of Health, Tokyo, Japan
Dr J. Kostrzewski (GC)	Secretary, Medical Section, Polish Academy of Sciences, Warsaw, Poland (*Chairman*)
Dr D. M. Mackay	Ross Institute of Tropical Hygiene, London School of Hygiene and Tropical Medicine, London, England (*Rapporteur*)

8. BURMA: 21–30 November 1977 (SEA/Smallpox/83)

Dr S. Jatanasen	Director, Division of Epidemiology, Ministry of Public Health, Bangkok, Thailand
Dr A. D. Langmuir	Professor, Harvard University Medical School, Department of Preventive and Social Medicine, Boston, MA, USA (*Secretary*)
Dr C. Lerche	Director, National Institute of Public Health, Oslo, Norway
Dr H. von Magnus	Head, Department of Epidemiology, State Serum Institute, Copenhagen, Denmark (*Rapporteur*)
Dr A. M. Mustaqul Huq	Director of Health Services (Preventive), Ministry of Health, Dhaka, Bangladesh
Dr I. F. Setiady	Director, Epidemiology and Quarantine, Ministry of Health, Jakarta, Indonesia (*Chairman*)
Dr M. I. D. Sharma	Emeritus Medical Scientist, New Delhi, India
Dr P. N. Shrestha (GC)	Chief, Smallpox Eradication Project, Department of Health Services, Kathmandu, Nepal
Dr U Thein Nyunt	Director, Disease Control, Ministry of Health, Rangoon, Burma

9. BANGLADESH: 1–14 December 1977 (SEA/Smallpox/84)

Dr S. Jatanasen	Director, Division of Epidemiology, Ministry of Public Health, Bangkok, Thailand
Dr A. D. Langmuir	Professor, Harvard University Medical School, Department of Preventive and Social Medicine, Boston, MA, USA (*Chairman*)
Dr C. Lerche	Director, National Institute of Public Health, Oslo, Norway
Dr H. von Magnus	Head, Department of Epidemiology, State Serum Institute, Copenhagen, Denmark (*Rapporteur*)
Dr A. M. Mustaqul Huq	Director of Health Services (Preventive), Ministry of Health, Dhaka, Bangladesh
Dr I. F. Setiady	Director, Epidemiology and Quarantine, Ministry of Health, Jakarta, Indonesia
Dr M. I. D. Sharma	Emeritus Medical Scientist, New Delhi, India
Dr P. N. Shrestha (GC)	Chief, Smallpox Eradication Project, Department of Health Services, Kathmandu, Nepal
Dr U Thein Nyunt	Director, Disease Control, Ministry of Health, Rangoon, Burma

10. MALAWI, MOZAMBIQUE, UNITED REPUBLIC OF TANZANIA and ZAMBIA: 6–29 March 1978 (AFR/Smallpox/87)

Dr M. Davies	Chief Medical Officer, Ministry of Health, Freetown, Sierra Leone
Dr Z. M. Dlamini	Senior Medical Officer of Health, Ministry of Health, Mbabane, Swaziland
Dr J. A. Espmark	Department of Virology, State Laboratory of Biology, Stockholm, Sweden
Dr F. Fenner (GC)	Director, Centre for Resource and Environmental Studies, The Australian National University, Canberra, Australia (*Rapporteur*)
Dr J. S. Moeti (GC)	Director of Medical Services, Ministry of Health, Gaborone, Botswana (*Chairman*)

11. IRAQ: 5–15 October 1978 (WHO/SE/78.127)
and
12. SYRIAN ARAB REPUBLIC: 15–22 October 1978 (WHO/SE/78.126)

Dr R. Netter (GC)	Director-General, National Health Laboratory, Paris, France (*Chairman*)
Dr M. Chamsa	Assistant Director, Organization of Medical Services, Red Lion and Sun Society of Iran, Teheran, Iran

13. UGANDA: 11–27 October 1978 (AFR/Smallpox/88)

Dr A. Deria (GC)	Director, Department of Public Health, Ministry of Health, Mogadishu, Somalia (*Chairman*)
Dr Kalisa Ruti (GC)	Medical Director, Expanded Programme on Immunization, Department of Public Health, Kinshasa, Zaire (*Rapporteur*)
Dr Y. P. Rikushin	Chief, Department of Epidemiology, Pasteur Institute, Leningrad, USSR

14. SUDAN: 15–29 November 1978 (WHO/SE/79.134)

Dr A. M. Fergany	Adviser, Ministry of Health, Oman (*Chairman*)
Dr W. Koinange (GC)	Chief Deputy Director of Medical Services, Ministry of Health, Nairobi, Kenya
Dr C. Lerche	Director, National Institute of Public Health, Oslo, Norway (*Vice-Chairman*)
Dr S. S. Marennikova (GC)	Chief, Laboratory of Smallpox Prophylaxis, Moscow Research Institute for Viral Preparations, Moscow, USSR
Dr G. Meiklejohn	Professor of Medicine, University of Colorado Medical Center, Denver, CO, USA (*Rapporteur*)
Dr D. A. Robinson	Community Physician, Communicable Disease Surveillance Centre, London, England
Ato Yemane Tekeste	Project Manager, Smallpox Eradication Programme, Addis Abeba, Ethiopia

15. ANGOLA: 5–16 February 1979 (AFR/Smallpox/89)

Dr Kalisa Ruti (GC)	Medical Director, Expanded Programme on Immunization, Department of Public Health, Kinshasa, Zaire (*Co-Rapporteur*)
Dr Bichat A. Rodrigues (GC)	Regional Coordinator for the South-East Region, Ministry of Health, Brasilia, Brazil (*Chairman*)
Dr Cabral A. J. Rodrigues	National Director of Preventive Medicine, Secretariat for International Cooperation, Maputo, Mozambique (*Co-Rapporteur*)

16. BOTSWANA, LESOTHO AND SWAZILAND: 5–23 March 1979 (AFR/Smallpox/90)

Dr D. Chilemba	Chief Medical Officer, Ministry of Health, Lilongwe, Malawi
Dr A. Deria (GC)	Director, Department of Public Health, Ministry of Health, Mogadishu, Somalia
Dr P. E. M. Fine	Ross Institute of Tropical Hygiene, London School of Hygiene and Tropical Medicine, London, England
Dr W. Koinange (GC)	Chief Deputy Director of Medical Services, Ministry of Health, Nairobi, Kenya (*Chairman*)
Dr G. Meiklejohn	Professor of Medicine, University of Colorado Medical Center, Denver, CO, USA (*Rapporteur*)

Dr E. A. Smith	Director of Medical Services, Federal Ministry of Health, Lagos, Nigeria
Dr I. Tagaya (GC)	Director, Department of Enteroviruses, National Institute of Health, Tokyo, Japan

17. DEMOCRATIC YEMEN: 3–11 June 1979 (WHO/SE/79.140)

Dr F. Jurji	Director of Epidemiology and Quarantine, Directorate General of Preventive Medicine, Ministry of Health, Baghdad, Iraq
Dr T. Kitamura	Chief, Division of Poxviruses, National Institute of Health, Tokyo, Japan (*Chairman*)
Dr V. Šerý	Chief, Department of Tropical Diseases, Postgraduate School of Medicine, Prague, Czechoslovakia

18. YEMEN: 2–10 June 1979 (WHO/SE/79.139)

Dr J. M. Aashi (GC)	Assistant Director-General of Preventive Medicine, Ministry of Health, Riyadh, Saudi Arabia (*Co-Chairman*)
Dr T. J. Geffen	Director, Communicable Diseases Division, Department of Health and Social Security, London, England (*Rapporteur*)
Dr R. Netter (GC)	Director-General, National Health Laboratory, Paris, France (*Co-Chairman*)

19. DJIBOUTI: 9–18 October 1979 (WHO/SE/79.147)

Dr N. C. Grasset	Epidemiologist, Douvaine, France; formerly Regional Adviser for Smallpox Eradication in the WHO Regional Office for South-East Asia, New Delhi, India (*Rapporteur*)
Dr T. Nacef	Director, Department of Preventive and Social Medicine, Ministry of Public Health, Tunis, Tunisia
Dr R. Netter (GC)	Director-General, National Health Laboratory, Paris, France (*Chairman*)

20. ETHIOPIA: Preliminary visit: 3–18 April 1979; final visit: 1–19 October 1979 (WHO/SE/79.148)

Dr R. N. Basu (GC)	Assistant Director-General of Health Services, Directorate General of Health Services, New Delhi, India
Dr Z. M. Dlamini	Director of Medical Services, Ministry of Health, Mbabane, Swaziland
Dr K. R. Dumbell (GC)	Head, Department of Virology, The Wright–Fleming Institute of Microbiology, St Mary's Hospital Medical School, London, England
Dr J. Kostrzewski (GC)	Secretary, Medical Section, Polish Academy of Sciences, Warsaw, Poland
Dr H. B. Lundbeck (GC)	Director, National Bacteriological Laboratory, Stockholm, Sweden
Dr T. Olakowski	Deputy Director, National Tuberculosis Institute, Warsaw, Poland
Dr N. A. Ward	Save the Children Fund, London, England

Final visit: 1–19 October 1979

Dr K. R. Dumbell (GC)	Head, Department of Virology, The Wright–Fleming Institute of Microbiology, St Mary's Hospital Medical School, London, England (*Rapporteur*)
Dr D. A. Henderson (GC)	Dean, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, MD, USA (*Rapporteur*)

Dr J. Kostrzewski (GC)	Secretary, Medical Section, Polish Academy of Sciences, Warsaw, Poland
Dr I. Noormahommed	Deputy National Director of Preventive Medicine, Ministry of Health, Maputo, Mozambique
Dr D. A. Robinson	Epidemiologist, Communicable Disease Surveillance Centre, London, England
Dr A. A. Stroganov	Assistant Professor, Central Institute for Advanced Medical Training, Communicable Disease Department, Moscow, USSR

21. KENYA: 1–19 October 1979 (WHO/SE/79.149)

Dr R. N. Basu (GC)	Assistant Director-General of Health Services, Directorate General of Health Services, New Delhi, India (*Chairman*)
Dr Kalisa Ruti (GC)	Medical Director, Expanded Programme on Immunization, Department of Public Health, Kinshasa, Zaire
Dr S. S. Marennikova (GC)	Chief, Laboratory of Smallpox Prophylaxis, Moscow Research Institute for Viral Preparations, Moscow, USSR
Dr G. Meiklejohn	Professor of Medicine, University of Colorado Medical Center, Denver, CO, USA (*Rapporteur*)
Dr J. S. Moeti (GC)	Senior Medical Officer of Health, Ministry of Health, Gaborone, Botswana

22. SOMALIA: 1 21 October 1979 (WHO/SE/79.146)

Dr J. M. Aashi (GC)	Assistant Director-General of Preventive Medicine, Ministry of Health, Riyadh, Saudi Arabia
Dr Z. M. Dlamini	Director of Medical Services, Ministry of Health, Mbabane, Swaziland
Dr T. J. Geffen	Director, Communicable Diseases Division, Department of Health and Social Security, London, England (*Rapporteur*)
Dr H. B. Lundbeck (GC)	Director, National Bacteriological Laboratory, Stockholm, Sweden (*Chairman*)
Dr J. D. Millar	Assistant Director for Public Health Practice, Center for Disease Control, Atlanta, GA, USA
Dr P. N. Shrestha (GC)	Chief, Planning Division, Tribhuvan University Institute of Medicine, Kathmandu, Nepal

ANNEX 24.2. PARTICIPANTS IN THE CONSULTATION ON THE WORLDWIDE CERTIFICATION OF SMALLPOX ERADICATION AND MEMBERS OF THE GLOBAL COMMISSION

The numbers in parentheses have the following significance:
(1) participated in the 1977 Consultation;
(2) attended the 1978 meeting of the Global Commission;
(3) attended the 1979 meeting of the Global Commission.

Participants in the Consultation and Members of the Global Commission

Dr J. M. Aashi (1, 2, 3)	Assistant Director-General of Preventive Medicine, Ministry of Health, Riyadh, Saudi Arabia
Dr J. Azurin (1, 2, 3)	Under-Secretary of Health, Department of Health, Manila, Philippines
Dr R. N. Basu (1, 2, 3)	Assistant Director-General of Health Services, Directorate General of Health Services, New Delhi, India

Dr P. N. Burgasov (2, 3)	Deputy Minister of Health, Moscow, USSR
Dr H. Corral (1)	Director-General, Ministry of Health, Quito, Ecuador
Dr A. Deria (1, 2, 3)	Director, Department of Public Health, Ministry of Public Health, Mogadishu, Somalia
Dr K. R. Dumbell (1, 2, 3)	Head, Department of Virology, The Wright–Fleming Institute of Microbiology, St Mary's Hospital Medical School, London, England
Dr F. Fenner (1, 2, 3; Chairman: 1, 2, 3)	Director, Centre for Resource and Environmental Studies, The Australian National University, Canberra, Australia
Dr D. A. Henderson (1, 2, 3)	Dean, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, MD, USA
Dr Kalisa Ruti (3)	Medical Director, Expanded Programme on Immunization, Kinshasa, Zaire
Dr J. Kilgour (1)	Head, International Health Division, Department of Health and Social Security, London, England
Dr W. Koinange (1, 2, 3; Vice-Chairman: 1)	Director, Division of Communicable Disease Control, Ministry of Health, Nairobi, Kenya
Dr J. Kostrzewski (1, 2, 3; Vice-Chairman: 2, 3)	Secretary, Medical Section, Polish Academy of Sciences, Warsaw, Poland
Dr H. B. Lundbeck (1, 2, 3)	Director, National Bacteriological Laboratory, Stockholm, Sweden
Dr S. S. Marennikova (1, 2, 3)	Chief, Laboratory of Smallpox Prophylaxis, Moscow Research Institute for Viral Preparations, Moscow, USSR
Dr J. S. Moeti (1, 2, 3)	Senior Medical Officer of Health, Ministry of Health, Gaborone, Botswana
Dr C. Mofidi (1, 2)	Minister of Higher Education and Science, Teheran, Iran
Dr R. Netter (1, 2, 3)	Director-General, National Health Laboratory, Paris, France
Dr Bichat A. Rodrigues (3)	Executive Secretary, National Council of Health, Brasilia, Brazil
Dr P. N. Shrestha (2, 3)	Chief, Planning Division, Tribhuvan University Institute of Medicine, Kathmandu, Nepal
Dr I. Tagaya (2, 3)	Director, Department of Enteroviruses, National Institute of Health, Tokyo, Japan
Dr P. F. Wehrle (1, 2, 3; Rapporteur: 1, 2, 3)	Hastings Professor of Pediatrics, Los Angeles County—University of Southern California Medical Center, Los Angeles, CA, USA
Dr Zhang Yihao (3)	Deputy Director, National Serum and Vaccine Institute, Beijing, China

WHO Advisers

Dr H. Corral (1)	Director-General, Ministry of Health, Quito, Ecuador
Dr W. H. Foege (2)	Director, Center for Disease Control, Atlanta, GA, USA
Dr T. J. Geffen (2)	Director, Communicable Diseases Division, Department of Health and Social Security, London, England
Dr N. C. Grasset (2)	Epidemiologist, Douvaine, France
Dr Jiang Yu-tu (3)	Military Academy of Medical Sciences, Beijing, China
Dr G. Meiklejohn (2, 3)	Professor of Medicine, University of Colorado Medical Center, Denver, CO, USA
Dr W. Nicol (2)	Area Medical Officer, Birmingham, England
Dr A. G. Rangaraj (2)	Epidemiologist, Nilgiris District, Madras, India
Dr Parviz Rezai (2)	Deputy Director-General, Communicable Diseases Control and Malaria Eradication, Ministry of Health and Welfare, Teheran, Iran
Ato Yemane Tekeste (2, 3)	Programme Manager, Smallpox Eradication Programme, Addis Abeba, Ethiopia

WHO Regional Office Staff

Africa:
Dr A. H. Abou-Gareeb (3), Director, Disease Prevention and Control, Brazzaville, Congo
Dr C. Algan (1, 2), Medical Officer, Health Services, Brazzaville, Congo
Dr Z. Islam (2, 3), Medical Officer, Epidemiological Surveillance of Communicable Diseases Project, Nairobi, Kenya
Dr L. N. Khodakevich (2, 3), Interregional Medical Officer, Smallpox Eradication Project, Addis Abeba, Ethiopia

Americas:
Dr J. Bond (3), Medical Officer, Communicable Diseases, Washington, DC, USA
Dr C. H. Tigre (2), Scientist, Communicable Diseases, Washington, DC, USA
Dr K. A. Western (1, 2), Chief, Communicable Diseases, Washington, DC, USA

South-East Asia:
Dr L. N. Khodakevich (1), Medical Officer, Smallpox Eradication, New Delhi, India

Europe:
Dr M. R. Radovanovic (1, 2), Medical Officer, Epidemiological Surveillance of Communicable Diseases, Copenhagen, Denmark

Eastern Mediterranean:
Dr P. Chasles (1), Medical Officer, Communicable Diseases Prevention and Control, Alexandria, Egypt
Dr F. Partow (2), Medical Officer, Communicable Diseases Prevention and Control, Alexandria, Egypt

Western Pacific:
Dr B. C. Dazo (3), Scientist, Communicable Diseases, Manila, Philippines
Dr R. R. Lindner (1), Medical Officer, Communicable Diseases, Manila, Philippines
Dr Chin Wentao (2), Consultant Medical Officer, Communicable Diseases, Manila, Philippines

WHO Headquarters Staff

Dr I. D. Ladnyi (1, 2, 3), Assistant Director-General
Dr A. Zahra (2, 3), Director, Division of Communicable Diseases
Dr I. D. Carter (2, 3), Epidemiologial Surveillance of Communicable Diseases
Dr H. J. Schlenzka (2), Legal Division
Dr E. Shafa (1, 2), Expanded Programme on Immunization

Smallpox Eradication unit:

Dr I. Arita (1, 2, 3), Chief Medical Officer
Dr J. G. Breman (1, 2, 3), Medical Officer
Mr R. N. Evans (2, 3), Technical Officer
Dr A. I. Gromyko (1, 2, 3), Medical Officer
Mr R. O. Hauge (1), Consultant Technical Officer
Dr Z. Ježek (2, 3), Medical Officer
Mr J. Magee (2, 3), Information Officer
Dr J. L. Tulloch (2, 3), Consultant Medical Officer
Mr. J. F. Wickett (1, 2, 3), Administrative Officer

CHAPTER 25

CERTIFICATION BY INTERNATIONAL COMMISSIONS: 1973–1977

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INTRODUCTION

In the previous chapter we examined in broad terms the process by which the certification of smallpox eradication was undertaken, culminating in the adoption by the World Health Assembly on 8 May 1980 of a resolution declaring that smallpox had been eradicated throughout the world. In the present chapter and the two which follow, this process is examined in more detail. It is evident that the problems that occurred paralleled those encountered during the elimination of smallpox from different countries. In this chapter an account is given of the activities of 9 international commissions which operated before the Consultation on the Worldwide Certification of Smallpox Eradication took place at WHO Headquarters in Geneva in October 1977. These include the 3 commissions which laid the foundation for all the others (see Chapter 24)—namely, those for South America, the first exploratory effort; Indonesia, a much more sophisticated procedure, but still in process of development; and western and central Africa, which set the pattern for the certification of many other countries in Africa and Asia from which smallpox had been eliminated several years earlier. The chapter closes with a brief de-

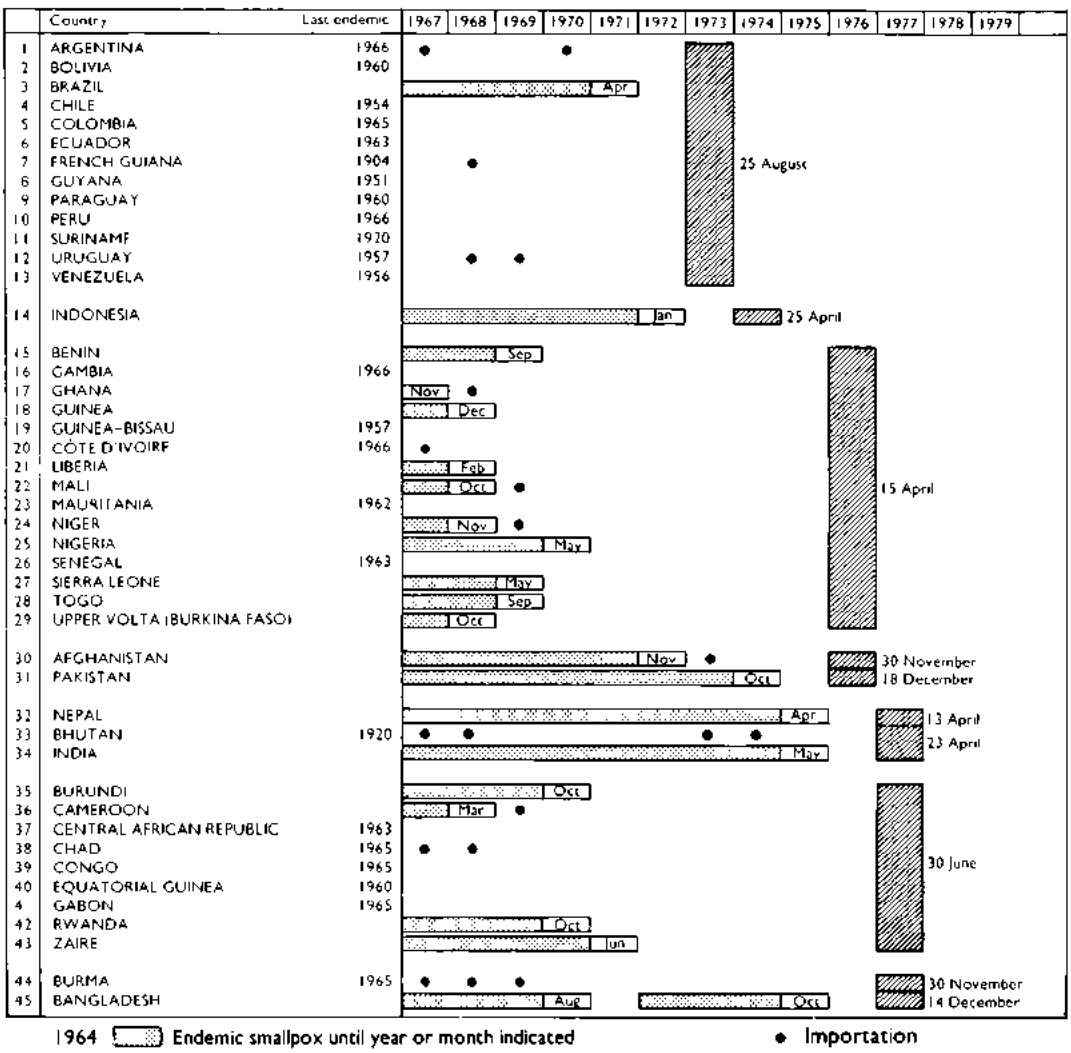

Fig. 25.1. Countries certified to be smallpox-free by international commissions operating between 1973 and 1977. The vertical boxes indicate the year in which the country was visited by an international commission; the dates on the right of these are those of the certification of the country or group of countries.

scription of the certification of the eradication of variola major from the world. This was carried out by the large international commissions which dealt first with Afghanistan and Pakistan in the west, and then with the principal and ancient home of variola major - India, Bangladesh and some of their small neighbours.

Fig. 25.1 shows the countries covered by these 9 international commissions, the month and year of the last cases in each country, and the dates of certification.

The special procedures adopted, the studies carried out and the factors which affected the decision by each of the international commissions to certify that eradication had been achieved are described in the sections which follow. Common to all countries, and of long standing, was the routine notification of a number of infectious diseases by hospitals and health centres, special attention being given to smallpox and the other diseases subject to the International Health Regulations (cholera, plague and yellow fever); all cases of these diseases had to be notified to WHO. Although the reporting of smallpox had been very incomplete when the Intensified Smallpox Eradication Programme began, the system then in place had served to detect and report cases in the endemic countries. During the course of the Intensified Programme, routine notification systems improved in all countries and, although they were not sufficiently sensitive to detect all the cases of smallpox that might have occurred, it was unlikely that any of them would fail to detect at least some of the numerous cases which would have had to occur if transmission was sustained over many years. The continuing absence of reports of cases of smallpox, often for a period of some years during which other diseases were being reported to WHO, increased confidence in the certification process, especially in countries in which certification was undertaken several years after the occurrence of the last known case of endemic smallpox.

CERTIFICATION IN SOUTH AMERICA

The last case of smallpox in South America was reported from Brazil in April 1971; South America was certified free of smallpox in August 1973.

Recent History of Smallpox

The history of smallpox in South America since the late 1950s has been described in Chapter 12. The essential features are summarized below as a background to the precertification activities and the recommendations of the Commission for the Assessment of the Smallpox Eradication Program in the Americas, which met in 1973.

After 1967, when the Intensified Smallpox Eradication Programme was initiated, only 3 countries in South America and the French Overseas Department of French Guiana reported cases of smallpox. The disease remained endemic in Brazil, which had long been reporting several thousand cases of variola minor annually, while Argentina, French Guiana, and Uruguay reported a few cases between 1967 and 1970, following importations from Brazil (Table 25.1). All the other South American countries had reported their last cases before 1967 (see Chapter 8, Fig. 8.6) and the last importation into the subcontinent from outside South America was believed to have occurred as long ago as 1920. Certification activities were therefore concentrated on Brazil and on adjacent countries in which importations from Brazil might have led to the establishment of new endemic foci.

Precertification Activities

In April 1971, the month in which the last outbreak of smallpox occurred in Brazil, it was decided that surveillance should continue

Table 25.1. South America: number of reported cases of smallpox, 1966–1972

Country	1966	1967	1968	1969	1970	1971	1972
Argentina	21	30[a]	0	0	24[a]	0	0
Brazil	3 623	4 514	4 372	7 407	1 771	19	0
French Guiana	0	0	1[a]	0	0	0	0
Peru	13	0	0	0	0	0	0
Uruguay	0	0	2[a]	3[a]	0	0	0

[a]Considered to be due to importation from Brazil.

in Brazil for 2 years after the occurrence of the last known case and that an assessment of the smallpox situation should then be made throughout South America (see Chapter 24). Over the next 2 years, country reports were prepared for submission to an independent assessment group by 11 countries (Argentina, Bolivia, Brazil, Colombia, Ecuador, Guyana, Paraguay, Peru, Suriname, Uruguay and Venezuela) and French Guiana; all of these except Brazil had been free of known endemic smallpox for at least 5 years. Chile was excluded because it had no common border with Brazil and, having a reasonably sophisticated health service infrastructure, had found no endemic smallpox to report since the early 1950s.

Brazil

The vaccination campaign carried out between 1967 and 1971 had covered over 80% of the Brazilian population of 97 million. As has already been mentioned, the last case of smallpox occurred in April 1971, in Guanabara State, but the campaign was continued until the International Commission's visit in 1973. By 1971, epidemiological surveillance units had been established in 2904 of the 3951 *municípios* (73%), and formed an important reporting network for suspected cases, the proportion of *municípios* with such units rising to 89% in 1972 and 90% by June 1973 (Table 25.2).

In 1972, health personnel conducted special inquiries aimed at collecting rumours of smallpox cases throughout the country. They interviewed personnel working in government agencies, such as political and health officials, schoolteachers and pupils, and workers in factories and businesses. More than 300 000 persons were interviewed in areas in which the risk of unreported cases of smallpox was believed to be the greatest (Table 25.3). This survey found 96 suspected cases, but none of them proved to be smallpox.

During the course of the organized surveillance programme between January 1971 and June 1973, 1293 suspected cases of smallpox were investigated (Table 25.4). Specimens

Table 25.2. Brazil: location and number of surveillance units in 1973

States and territories	Number of *municípios*	Number of surveillance units	Coverage (%)
North:			
Rondônia	2	2	100
Acre	7	7	100
Amazonas	44	30	68
Roraima	2	2	100
Pará	83	65	79
Amapá	5	5	100
North-east:			
Maranhão	129	129	100
Piauí	114	93	82
Ceará	142	130	92
Rio Grande do Norte	150	150	100
Paraíba	171	153	90
Pernambuco	164	164	100
Alagoas	94	94	100
Fernando de Noronha	1	1	100
Sergipe	74	74	100
Bahia	336	249	74
South-east:			
Minas Gerais	722	506	70
Espírito Santo	53	53	100
Rio de Janeiro	63	63	100
Guanabara	1	1	100
São Paulo	571	571	100
South:			
Paraná	288	281	98
Santa Catarina	197	197	100
Rio Grande do Sul	232	230	97
Central-west:			
Mato Grosso	84	82	98
Goiás	221	221	100
Distrito Federal	1	1	100
Brazil, total	3 951	3 554	90

Table 25.3. Brazil: results of survey conducted in high-risk areas in 1972

Personnel category or establishment	Number of persons interviewed	Number of suspected cases[a]
Political officials	1 309	1
Health officials	2 535	3
Health services	15 579	2
Private medical services	5 378	1
Public records offices	561	6
Factories or business enterprises	45 605	1
Schools (teachers and pupils)	125 920	19
Other	120 405	63
Total	317 292	96

[a] None found to be smallpox.

Table 25.4. Brazil: investigations of suspected cases of smallpox, 1971–1973

States and territories	1971			1972			1973		
	Number of suspected cases	Number investigated	Number of laboratory tests	Number of suspected cases	Number investigated	Number of laboratory tests	Number of suspected cases	Number investigated	Number of laboratory tests
North:									
Rondônia	0	0	0	0	0	0	0	0	0
Acre	0	0	0	0	0	0	0	0	0
Amazonas	0	0	0	4	4	4	0	0	0
Roraima	0	0	0	0	0	0	0	0	1
Pará	0	0	0	5	5	5	0	0	0
North-east:									
Maranhão	10	10	4	8	8	5	0	0	0
Piauí	2	2	2	30	30	7	5	5	0
Ceará	20	20	15	5	5	4	7	7	6
Rio Grande do Norte	0	0	0	0	0	1	3	3	0
Paraíba	1	1	0	5	5	3	0	0	0
Pernambuco	18	18	9	76	76	34	16	16	12
Alagoas	0	0	0	3	3	4	2	2	1
Fernando de Noronha	0	0	0	0	0	0	0	0	0
Sergipe	5	5	5	11	11	2	6	6	2
Bahia	22	16	18	59	59	26	11	11	8
South-east:									
Minas Gerais	32	32	24	39	39	50	14	14	10
Espírito Santo	31	31	27	19	19	33	4	4	4
Rio de Janeiro	26	26	18	48	48	26	9	9	4
Guanabara	35	35	25[a]	181	181	29	9	9	0
São Paulo	118	118	80	124	124	64	16	16	18
South:									
Paraná	42	42	35	37	37	38	1	1	2
Santa Catarina	9	9	6	13	13	7	11	11	8
Rio Grande do Sul	63	63	40	40	40	24	15	15	18
Central-west:									
Mato Grosso	0	0	0	7	7	3	2	2	3
Goiás	11	11	10	4	4	6	0	0	0
Distrito Federal	5	5	2	0	0	0	0	0	0
Brazil, total	450	444	320	718	718	375	131	131	97

[a] Including 19 confirmed cases from the last outbreak of smallpox in Brazil.

were collected for laboratory diagnosis from 792 of them; all gave negative results except the 19 specimens collected in Guanabara State during the last outbreak, which were positive. No evidence of smallpox transmission was found after April 1971.

Argentina

The last case in Argentina occurred in April 1970, in an outbreak of 24 cases in Misiones Province, which borders on Brazil. This began with an importation from Brazil

and was contained by mass vaccination as soon as it was discovered. By the end of 1971 the vaccination campaign in the province had reached 84% of the population of 443 020 persons. During the summer of 1971 Dr Claudio Marcos da Silveira, a WHO consultant, visited Argentina to assess the smallpox situation. With Dr Juan José Hiriart, chief of the national smallpox eradication programme, he contacted schoolteachers, health officers and community leaders in areas in which cases of smallpox had been reported between 1965 and 1970, paying special attention to the community of Colonia Alicia, in which the 1970 outbreak had occurred. A survey in these areas showed that 88% of the 2819 schoolchildren examined had vaccination scars. Investigation of 26 cases of fever with rash led to the diagnosis of chickenpox in all of them. No cases of smallpox were found.

Colombia

The last cases of smallpox had occurred in Colombia in 1965. Between 1967 and 1972 more than 13 million of the 22 million people in the country were vaccinated, and a survey in 1970 found that 70% of the age group 0–4 years, 85% of the age-group 5–14 years and 77% of those aged 15 years and over had vaccination scars. Vaccination coverage was satisfactory except in 6 sparsely settled departments in the Amazon region. No evidence of recent smallpox was found during the vaccination scar survey.

In November 1971 a special survey was conducted in the Amazon basin in the Commissary of Vaupés (90 000 square kilometres), one of the more isolated areas, adjacent to the Brazilian Amazon basin. It was found that in the previous year, 8 cases of fever with rash had occurred in the San Jorge District on the bank of the Vaupés river opposite the town of Mitú. These had been diagnosed as smallpox in the hospital at Mitú, but the investigation revealed that 4 of them were in persons who had been previously vaccinated and that all were cases of chickenpox. A further search for cases of fever with rash found no evidence of smallpox in this area.

French Guiana

No cases of smallpox had been recorded in the files of the public health authorities of French Guiana since 1904. One case imported from Brazil into Cayenne had occurred in 1968 but it did not appear in the official records although it had been reported to WHO. Dr Marcos da Silveira visited the territory as a WHO consultant in 1971 and concluded that continued smallpox transmission was most unlikely for two reasons. First, the population was small (44 000), the reporting system was reasonably good and, although there was a risk of importation through persons entering illegally from Brazil, the areas adjacent to Brazil were so thinly populated that it was unlikely that an endemic focus could be established. Secondly, the vaccination programme was continuing and the records showed that in 1970 nearly half the children under 1 year of age had been vaccinated; this suggested that the coverage of the older age groups should have been reasonably good.

Paraguay

The last outbreak of 32 cases in Paraguay followed an importation from Brazil in 1965. In 1971 an investigation was conducted by a team of WHO operations officers and national personnel in the areas at highest risk, all of which bordered on Brazil. The survey team travelled 5000 kilometres, visited 88 localities, interviewed 125 health personnel and 451 teachers and educational personnel, and discovered 15 cases of exanthematous diseases, all of which had occurred during the previous 12 months. These cases and an additional 50 persons with a history of attacks of fever with rash were investigated, but no cases of smallpox were found.

Nor was evidence of smallpox found in a national survey of schoolchildren, conducted in 336 schools throughout the country in 1971. During the course of routine spraying operations in May of that year, the malaria control service personnel also conducted a search for smallpox cases among a population which comprised 4% of the national total, but found none. To determine the vaccination coverage, a special scar survey was conducted in May–June 1971 among 19 470 persons in the south of Paraguay. It was found that 78% had vaccination scars; the proportion was 43% in the age group 0–4 years and more than 82% in those aged over 4 years.

Peru

The 13 cases which occurred in Peru in 1966 were the last in a large outbreak of

variola minor that began in 1963, following an importation from Brazil. A vaccination campaign carried out between 1968 and 1970 resulted in a good coverage of the population, as was shown by a vaccination scar survey of 30 000 persons that was conducted in 1970. It was found that 82% of the age group 0–4 years, 92% of the age group 5–14 years and 91% of adults bore scars. The vaccination teams found no evidence of smallpox during the campaign.

Uruguay

The last importation of smallpox into Uruguay was recorded in 1969, before which there had been importations annually between 1960 and 1965 and again in 1968. Each case had been carefully investigated in order to determine the source of infection and each outbreak had been traced to a person exposed in Brazil. The prompt reporting and careful epidemiological investigations gave grounds for confidence that the health authorities would have detected and reported other cases had they occurred. In 1971 a small vaccination scar survey was conducted; of the 1029 persons examined, 98% had been vaccinated.

Other countries

Bolivia, Chile, Ecuador, Guyana, Suriname and Venezuela had also conducted good vaccination programmes (see Chapter 12), and the most recent cases in each country were associated with importations. Bolivia reported its last case in 1964, Chile in 1963, Ecuador in 1963, Guyana in 1951, Suriname in 1920, and Venezuela in 1962; indigenous transmission had been interrupted in most of these countries several years earlier (see Chapter 8, Fig. 8.6).

In 1971 special vaccination and search programmes were carried out in the Amazon basin areas of Bolivia, Ecuador and Venezuela, in parallel with those conducted in Brazil and Colombia. No cases of suspected smallpox were found.

Visit of the International Commission

The Commission for the Assessment of the Smallpox Eradication Program in the Americas, as it was called, first met in Rio de Janeiro on 15 August 1973, and discussed the reports that had been prepared by each of the 11 countries and by French Guiana. The Commission was charged, as were all those that followed it, with the responsibility of reaching one of two possible conclusions: that it was satisfied that smallpox eradication had been achieved, or that it would be satisfied that smallpox eradication had been achieved if a specifically described set of activities were conducted and no further cases discovered.

The Commission split up into teams which visited several areas of epidemiological importance in Brazil. They participated in the epidemiological investigation of suspected cases of smallpox and observed the operation of the existing epidemiological surveillance system. The Commission held its final meeting in Brasilia on 25 August. As has been pointed out in Chapter 24, the constitution of this first international commission was not ideal, nor did it carry out its work with the same thoroughness as later international commissions.

The Commission reviewed the situation in the various countries. Its conclusions may be summarized as follows:

(1) Although the vaccination campaigns conducted in the 1960s throughout South America were in general satisfactory, protection was generally insufficient in children under 5 years of age and in areas to which access was difficult. The Brazilian campaign was regarded as notable for having reached high levels of vaccination coverage throughout the country and in all age groups.

(2) There was a need to improve the reporting system in certain areas. However, the Commission was impressed with the excellent epidemiological surveillance throughout Brazil, where there was a widespread network of reporting posts covering 90% of the *municipios* of the country.

(3) While the larger South American countries and Uruguay maintained services for the laboratory diagnosis of smallpox and, following the last reported case in April 1971, laboratory confirmation of the diagnosis of every suspected case was important, the quality of the laboratory work was not as satisfactory as might have been hoped. The Commission drew attention to certain deficiencies in the collection, packaging and shipment of specimens, which sometimes made laboratory diagnosis difficult. It also observed that there was no interchange of information between laboratories, even within the same country. Although the WHO

collaborating centre in Atlanta, USA, had agreed to test specimens, few specimens were submitted between 1967 and 1977 and most of them were from Brazil (Table 25.5).

(4) Although vaccine production in various countries in South America was sufficient to cover local needs, some countries continued to produce liquid vaccine intended for use wholly or in part in their respective jurisdictions. Even when it was freeze-dried, the quality was often not satisfactory; this applied, in particular, to the heat stability of egg vaccine produced in Brazil (see Chapter 12). Few laboratories regularly sent vaccine specimens for quality control to the WHO Reference Centre for Smallpox Vaccine for the Region of the Americas in Toronto, Canada.

Despite the deficiencies mentioned above, the Commission concluded that smallpox transmission had been interrupted in the region, but took a cautious approach to post-eradication policy, recommending that:

(1) Countries should continue to give due attention to reporting systems and to their improvement, particularly in areas in which reporting was weak, so that consistent information was immediately available on every suspected case.

(2) A sufficient number of adequately trained epidemiologists should be made available for epidemiological surveillance services, so that each case of suspected smallpox might be thoroughly investigated by a competent epidemiologist and specimens, taken under satisfactory conditions, sent to a laboratory.

(3) Smallpox having been eliminated from the Region of the Americas, and the laboratory investigation of every suspected case being of fundamental importance to epidemiological surveillance, the Pan American Health Organization should stimulate the establishment of a system designed to ensure the technical proficiency of the laboratories performing smallpox diagnostic procedures.

(4) In order to ensure that the vaccines produced in the region were of high quality, samples of 3 consecutive lots of vaccine should be sent every 4 months to the reference laboratory for quality control tests.

In essence, the Commission recommended that vaccination and surveillance activities should be continued in much the same way as before eradication. Since it was agreed that there was little likelihood of importing smallpox from another continent, this recommendation reflects a certain lack of confidence in the decision that smallpox transmission had been interrupted. Such caution is understandable; this was the first time that smallpox eradication had been certified, and the disease had been endemic in South America for more than 400 years.

CERTIFICATION IN INDONESIA

Although Indonesia was geographically close to the endemic countries of south-eastern Asia, no importation of smallpox had been recorded from them since 1949. It was therefore considered reasonable to undertake the certification of the eradication of smallpox in Indonesia in 1974, 2 years after the last known case.

Recent History of Smallpox

Smallpox was reintroduced into Indonesia in 1947, but it remained confined to the larger islands of the western part of the archipelago

Table 25.5. Numbers of specimens from suspected cases of smallpox received by the WHO collaborating centre, Atlanta, USA, from countries in South America, 1967–1977[a]

Year	Bolivia	Brazil	Colombia	Guyana	Uruguay	Venezuela
1967–1968	2	154	7	5	1	0
1969	1	0	0	5	0	0
1970	0	14	0	1	0	0
1971	4	0	0	0	0	4
1972	0	0	0	0	0	1
1973	0	0	0	0	0	0
1974	0	0	0	0	0	0
1975	0	0	0	0	0	1
1976	0	0	0	0	0	0
1977	0	0	0	0	0	1
Total	7	168	7	11	1	7

[a] All negative for variola virus.

(see Chapter 13, Fig. 13.3). The numbers of cases in these islands between 1967 and 1973 are shown in Table 25.6. The last case of smallpox in the country occurred in January 1972, in a village some 30 kilometres from Jakarta, West Java.

Precertification Activities

Smallpox surveillance continued until April 1974, when the International Commission visited Indonesia. In collaboration with national staff, WHO smallpox eradication programme staff—namely, Dr Giuseppe Cuboni (May 1971–October 1974) and Mr William Emmet (August 1970–July 1974)—continued to help with precertification surveillance.

In August 1973, Dr Paul Wehrle, a WHO consultant, visited Indonesia to review the progress of certification activities and to advise on other steps to be taken in order to demonstrate convincingly that eradication had been achieved. He visited 26 provinces in North Sumatra, South Sulawesi, West Java and West Kalimantan to assess surveillance activities, using as indices the regularity with which the weekly smallpox reports were submitted, the number of notifications and the number of laboratory samples collected and tested. He reported that he was personally convinced that smallpox transmission had been interrupted in Indonesia but recommended various measures to improve surveillance.

Neither the activities of the national eradication programme nor those of the International Commission subsequently covered all the thousands of small islands in the archipelago. After 1949, no smallpox cases had been reported from any of the islands east of Sulawesi and Nusa Tenggara, although authorities on these islands routinely reported cases of other diseases. If smallpox had occurred there, rumours would have come to the notice of the health service. Experience in many islands in the South Pacific had shown that smallpox transmission could not be maintained on isolated oceanic islands because the populations were too small to provide a continuous supply of susceptible persons. The small islands of the Indonesian archipelago had apparently been free from smallpox for several decades, and the chance of continuing endemicity there was considered to be nil.

Special searches

Between March and December 1972 visits to the villages in which cases of smallpox had occurred during the period 1970–1972 were carried out by surveillance teams, consisting of national, provincial and regency smallpox eradication programme staff, in 11 provinces of Java, Sulawesi and Sumatra (Fig. 25.2). The main purpose of these visits was to ensure that the recent smallpox outbreaks had been thoroughly contained. In addition, rumours about suspected cases in localities or areas in frequent contact with those affected were investigated. Other localities that were searched were those that did not report regularly, those that were seldom visited by health personnel, and those in which frequent staff changes suggested some weakness in the local health services.

During these special searches, 1352 villages were visited and the civil authorities, religious leaders and the security forces questioned, and inquiries were made at health centres and schools. Of 650 reports of cases of suspected smallpox discovered, 629 proved to be cases of chickenpox; none was smallpox. Approximately 180 laboratory specimens were collected and tested by Indonesian laboratories, all with negative results. The

Table 25.6. Indonesia: number of reported cases of smallpox in various islands, 1967–1973

Island	1967	1968	1969	1970	1971	1972	1973
Bali	43	0	0	0	0	0	0
Java	10 067	15 654	14 069	4 648	195	34	0
Kalimantan	537	81	41	0	0	0	0
Sulawesi	670	101	833	1 721	1 451	0	0
Sumatra	962	1 514	3 029	3 712	454	0	0
West Nusa Tenggara	1 199	0	0	0	0	0	0
Others	0	0	0	0	0	0	0
Total	13 478	17 350	17 972	10 081	2 100	34	0

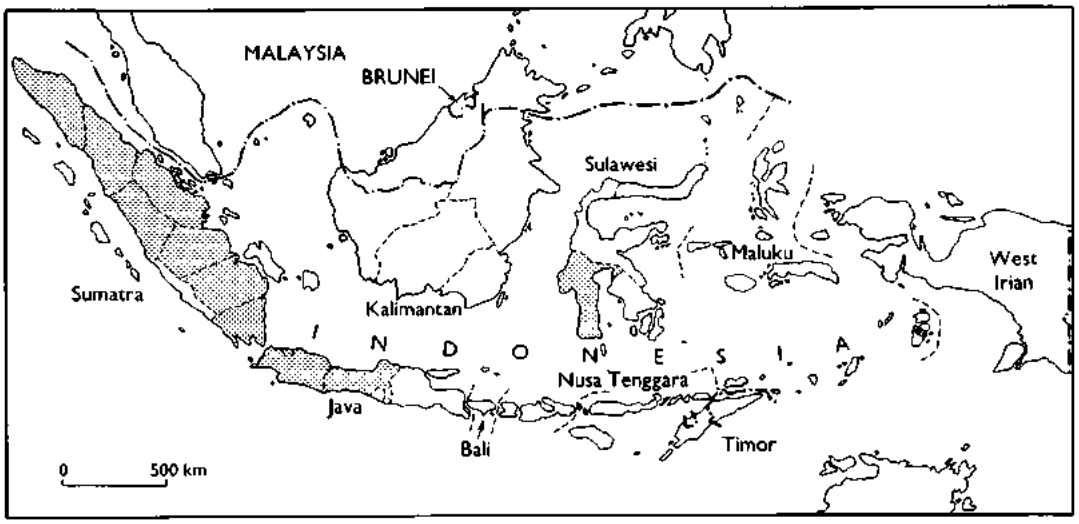

Fig. 25.2. Provinces of Indonesia in which cases of smallpox were reported between 1970 and 1972. Special searches were conducted in all these provinces (shaded).

special searches failed to elicit any evidence of the occurrence of smallpox after January 1972.

Reward for smallpox detection

In May 1972, immediately after the last known case has been detected, the Indonesian government offered a reward of 5000 rupiahs (US$12) to any person reporting a case of smallpox which was confirmed by laboratory tests. A similar amount was to be given to the first health worker who investigated and confirmed the case. The reward was given wide publicity by health workers when talking to the public during field visits (see Chapter 10, Plate 10.8C) in the hope of urging people to reveal rather than hide any new case.

Routine reporting of suspected cases

The existing system for the routine weekly reporting of suspected smallpox cases was strengthened. In 1972, roughly 20% of the expected number of weekly reports were submitted, whereas in 1974 the level had risen to 50% at both the regency and provincial levels. Between 1972 and 1974, 6186 cases of suspected smallpox were reported and 8505 cases investigated (Table 25.7), the latter number including additional suspected cases discovered during the investigations of the original cases. As usual, the disease most frequently mistaken for smallpox was chickenpox, which accounted for about 70% of the total suspected cases seen, other skin diseases (scabies, measles, impetigo and dermatitis) accounting for the remainder.

Laboratory diagnosis

After what was thought to be the last case of smallpox in Indonesia had been reported in 1972, the laboratory investigation of suspected smallpox became of vital importance. The number of specimens collected in various

Table 25.7. Indonesia: routine reporting of cases of suspected smallpox, May 1972–February 1974

Year	Number of suspected cases					Source of reports (%)			
	Reported	Total investigated	Chicken-pox	Smallpox	Others	Health personnel	Civil authorities	Members of the public	Unspecified
1972	2 298	3 223	2 236	0	987	38	27	25	10
1973	3 067	4 175	2 781	0	1 394	38	31	18	13
1974	821	1 107	613	0	494	44	26	21	9
Total	6 186	8 505	5 630	0	2 875	–	–	–	–

geographical areas was considered to be an index of the sensitivity of the surveillance system. Laboratory tests (gel precipitation and virus isolation) were carried out locally at the Biofarma Virological Laboratory in Bandung or the Central Public Health Laboratory in Jakarta, but specimens considered to be of special importance were also investigated by the WHO collaborating centres. In spite of the time required for shipment and communications—from the field to Jakarta, then to Geneva, then to a collaborating centre in the USA or USSR, and back by the same route—the results of tests carried out at the collaborating centres were available to the field staff within 5 weeks of the specimen being collected in 1972 and within 4 weeks in 1973 and 1974.

In addition to collecting laboratory specimens from all suspected smallpox cases, from September 1972 onwards health personnel were instructed to collect specimens from clinically unequivocal chickenpox in persons over 14 years of age who had no evident vaccination scar and from persons who had become ill in an outbreak of chickenpox in which a death had occurred. This type of surveillance was introduced after the last smallpox outbreak, in which cases had been reported to resemble chickenpox.

Between 1971 and 1973, altogether 1758 specimens were tested (Table 25.8), none being found positive for smallpox after 1972. Since chickenpox virus did not grow on the chorioallantoic membrane, hundreds of specimens from chickenpox viruses might be examined with consistently negative results. To encourage the laboratory workers and to test the laboratories' ability to grow poxviruses on the chorioallantoic membrane, samples were occasionally submitted from vaccinial lesions, from which vaccinia virus could be grown; this explains the positive results for vaccinia virus in 1972 and 1973 shown in Table 25.8.

Table 25.8. Indonesia: laboratory diagnosis of suspected cases of smallpox, 1971–1973[a]

Year	Number of specimens	Number positive for:	
		variola virus	vaccinia virus
1971	150	15	0
1972	1 009	12	1[b]
1973	599	0	6[b]
Total	1 758	27	7

[a] Biofarma, Bandung, tested 1479 specimens, the Central Public Health Laboratory, Jakarta, 247 specimens and WHO collaborating centres 32 specimens.

[b] From samples from vaccinial lesions, submitted as a means of checking the ability of the laboratory to grow poxviruses on the chorioallantoic membrane.

Local declaration of smallpox-free status

The national programme director decided that the local authorities should be responsible for confirming that smallpox was no longer prevalent in the areas under their jurisdiction. A total of 12 provinces in Java, Sulawesi and Sumatra had been defined as areas of concern, since cases of smallpox had been reported from them after 1970. In these provinces, both the civil authorities and the health service representatives of every village or area were requested to sign a document declaring that that locality was free of smallpox. Before this document was signed, every village chief and his local medical staff were given 2 weeks in which to check the area carefully and report any suspected case to the nearest health centre. However, the signing of the statement did not remove the duty to report any suspected case. On the contrary, all those involved were informed about the dangers of importation and the need for vigilance. This process was started in April 1973 and concluded in April 1974, involving 12 of the 26 provinces, as already mentioned, 158 of the 288 regencies and municipalities, 1771 of the 3203 subdistricts and about 25 000 of the 46 396 villages (*desas*) in Java, Sulawesi and Sumatra—a formidable task that required considerable organizational effort and logistic support.

These precertification efforts drew attention to smallpox and increased awareness of the reward offered both to health workers and to the general public for the notification of a case that could be confirmed.

Special survey in Kalimantan and Sulawesi

The health services in Kalimantan and Sulawesi were less well developed than those in Java and Sumatra; both islands had recently experienced smallpox and both were difficult places in which to work. In February and March 1974 special searches for smallpox, involving pockmark and vaccination scar surveys in the age group 0–14 years, were therefore carried out in these islands. South Sulawesi, in which the last endemic cases had

been reported, was not visited, since an intensive eradication programme had been conducted there, followed by intensive surveillance. Primary schools and health centres were visited in the towns and large villages of 7 provinces of Kalimantan and Sulawesi, and inquiries made about smallpox rumours. It was considered that the epidemiological situation in these towns and villages, which were located in coastal areas and on rivers and served as communication centres for remote areas, would reflect that in the inland part of the islands which, because of limitations of time, funds and manpower, could not be searched.

A total of 27 538 children aged 0–14 years were examined in 22 selected localities. No facial pockmarks were found in the age group 0–4 years, while there were 27 pockmarked children in the age group 5–14 years, none of whom had had smallpox during the previous 2 years. This strengthened confidence that both Kalimantan and the selected provinces of Sulawesi had been free of smallpox since 1970. Vaccination scars were found in 26% of children in the age group 0–1 year, 58% in the age group 1–4 years, and 83% in the age group 5–14 years. These levels of vaccination coverage were not satisfactory but, in view of the low population density in these islands and their isolation from the main endemic areas of Java, it was thought likely that smallpox transmission there had been interrupted in 1969.

Visit of the International Commission

On 15 April 1974, 26 months after the last case of smallpox had been reported from Indonesia, the International Commission for the Certification of Smallpox Eradication (Plate 25.1) met in Indonesia. Dr Wehrle, who was well informed about the activities that had been undertaken in Indonesia and was thus in a position to guide the deliberations of the Commission, acted as chairman. After some discussion among the other members of the Commission, Dr Julie Sulianti Saroso, Director-General for the Control and Pre-

WHO

Plate 25.1. Participants in the meeting of the International Commission for the Certification of Smallpox Eradication in Indonesia, 25 April 1975. *Left to right, front row:* **J.J. Dizon (Philippines), J. Sulianti Saroso (Indonesia), P.F. Wehrle (USA)**, A. Karyadi (Indonesia); *middle row:* B. Cantayuda (Indonesia), **I. Tagaya (Japan), N.McK. Bennett (Australia), J.S. Gill (Malaysia), S. Kumarapathy (Singapore)**; *back row:* N. Kumara Rai (Indonesia), G.G.O. Cuboni (WHO), I.F. Setiady (Indonesia), D.A. Henderson (WHO), J. Keja (WHO). The names of the Commission members are in bold type.

vention of Communicable Diseases in the Indonesian Ministry of Health, was included as a member. This arrangement might be thought to have reduced the objectivity of the Commission's assessment but, on the other hand, her presence provided additional assurance that no areas of the country would be barred to members of the Commission (see Chapter 24). After the first meeting in Jakarta, the members of the Commission, accompanied by programme staff, left for the areas judged most likely to harbour smallpox cases—namely, Jakarta, North Sumatra, South Sulawesi and West Java, which were visited during a period of 2 weeks (Fig. 25.3). In their field work, the members concentrated on assessing the extent and sensitivity of the surveillance activities and reporting system, as well as on examining health records and interrogating health service staff and the public. They visited as many localities as possible, searching for patients suffering from fever with rash, whom they examined to ensure that they did not have smallpox. The Commission then held its final meeting in Jakarta on 24 and 25 April 1974. Having concluded that there was no evidence that smallpox had occurred in Indonesia since January 1972 and that surveillance activities appeared to have been adequate to identify cases had they occurred, it approved the certification of the eradication of smallpox in Indonesia as a whole.

Because of the continuing high incidence of smallpox in the Indian subcontinent and the consequent risk of importations, the Commission strongly emphasized that "continuing vigilant surveillance and evaluation are necessary for all persons with illnesses suspected as smallpox", and recommended that "primary vaccination of infants and children against smallpox should be continued until global eradication of smallpox has been achieved".

CERTIFICATION IN AFRICA SOUTH OF THE SAHARA

The organization of certification in Africa south of the Sahara constituted a special challenge for a number of reasons. The region contained 42 countries which had previously been endemic, or whose neighbours had previously been endemic, and had become smallpox-free between 1967 and 1977 (Fig. 25.4). Communication within and between many of these countries was difficult, and the health service infrastructure in most of them was at a rudimentary stage of development. The certification programme was implemented by grouping countries together geographically and on the basis of similar histories of the elimination of smallpox. One such grouping, western Africa, comprising 15 countries, was the first in which the feasibility of certification of a regional group was tested (see Chapter 24); this was followed by the certification of 9 countries in central Africa.

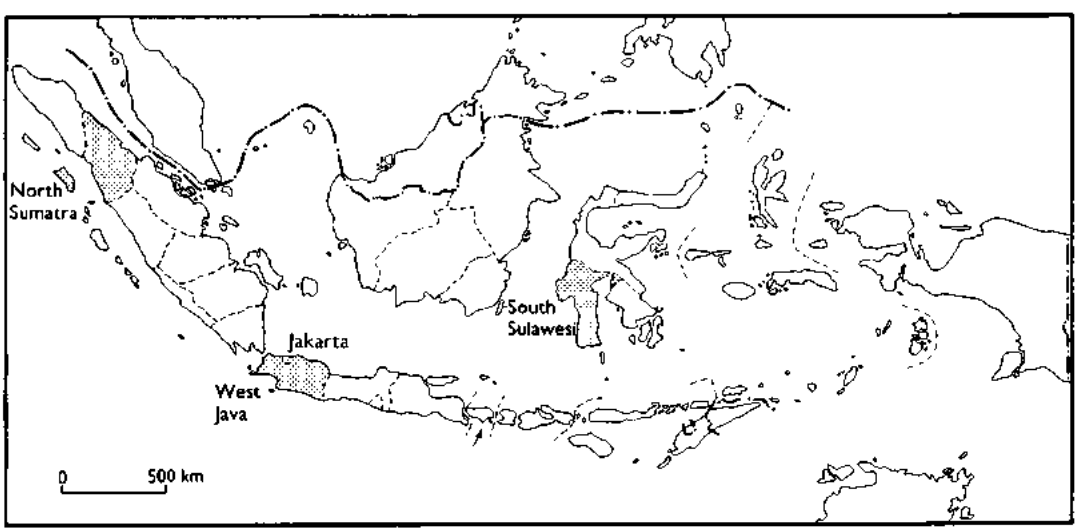

Fig. 25.3. Provinces of Indonesia (shaded) visited by members of the International Commission, 15–25 April 1974.

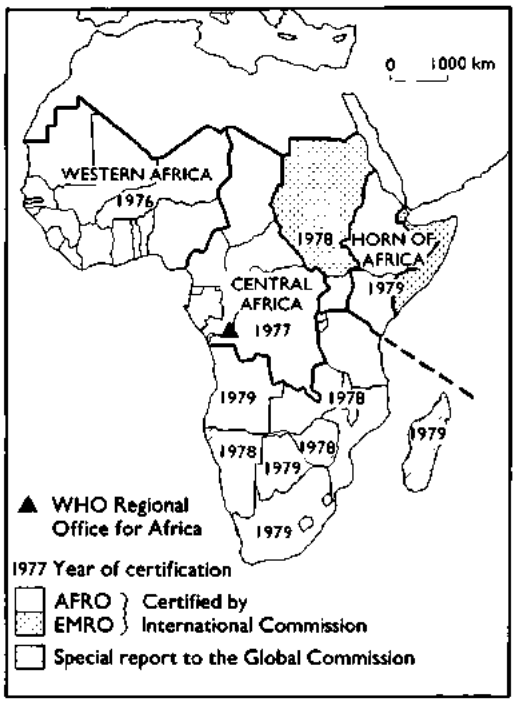

Fig. 25.4. Organization of certification in Africa south of the Sahara. A total of 42 countries were the subject of special certification procedures, 39 of them being in the WHO African Region and 3 (Djibouti, Somalia and Sudan) in the WHO Eastern Mediterranean Region. During 1976–1979 the certification programme was implemented by grouping countries together on the basis of geographical and epidemiological criteria.

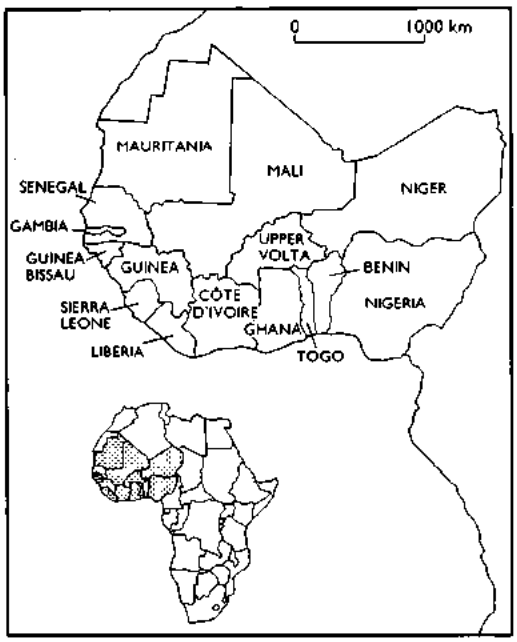

Fig. 25.5. The 15 countries of western Africa which were certified free of endemic smallpox by the International Commission in April 1976. Upper Volta is now Burkina Faso.

Arrangements based on the epidemiological and political situation in another 14 countries in eastern and southern Africa led to their certification in 1978 and 1979, by a variety of methods (see Chapter 26). The 4 remaining countries in the Horn of Africa, as the last group, were eventually certified by international commissions in October 1979 (see Chapter 27).

WESTERN AFRICA

In western Africa, 15 countries—Benin, Côte d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone, Togo and Upper Volta (now Burkina Faso) (Fig. 25.5)—shared many features which made it logical to group them for the certification of smallpox eradication.

As has been described in Chapter 17, smallpox eradication and measles control programmes had been carried out in the region with United States support, and the last known outbreak of endemic smallpox had occurred in April 1970. Intensive surveillance had continued, with bilateral assistance, for more than 2 years thereafter, but both surveillance and the extent of vaccination had declined sharply after the assistance ceased. By 1976, when the International Commission for the Certification of Smallpox Eradication was scheduled to visit the region, the staff who had worked in the campaign had become involved in other activities or gone elsewhere, records were scattered or lost and smallpox surveillance activities had diminished. Because smallpox had been absent from these countries for more than 5 years, and because health services in western Africa were much less well developed than those in South America and Indonesia, it was decided that the surveys and documentation required before the Commission's visit could be—and, indeed, would have to be—simpler and adapted to the local situation.

Recent History of Smallpox

The eradication campaign in these countries has been described in Chapter 17. Data on the numbers of cases reported between 1966 and 1971 are shown in Table 25.9. Unlike certain other regions of Africa, western Africa had experienced only variola major, usually associated with a somewhat lower case-fatality rate than in the Indian subcontinent. Hence facial pockmark surveys provided a valuable means of assessing the past prevalence of the disease.

Variolation had formerly been widely practised in many countries in the region (Herbert, 1975), but in the 1960s it was observed only in a few localized areas, the last being in Dahomey (Benin) in 1969.

Preparations for Certification

Planning meeting, 3–6 February 1975

In order to plan a strategy for the certification of smallpox eradication in Africa, a meeting was held at the WHO Regional Office for Africa in Brazzaville, Congo, from 3 to 6 February 1975. It was attended by Dr Celal Algan, Regional Adviser on Communicable Diseases, Arita from the Smallpox Eradication unit at WHO Headquarters, and Dr Wehrle, the WHO consultant mentioned earlier in this chapter who had assisted with the planning of certification activities in Indonesia, together with other WHO staff.

The meeting agreed with the proposal that certification should start with the 15 countries of western Africa, since importations were very unlikely from Ethiopia, the only African country in which smallpox was then still endemic, as it was 1500 kilometres away and there was little communication between the two areas.

Decisions were reached on 3 matters: local funding, coordination of precertification activities and the preparation of country reports. For most countries, WHO agreed to provide funds to cover the local travelling expenses (living allowances, petrol and oil) of mobile teams carrying out pockmark surveys. The other matters required continuing attention, as described below.

Coordination of precertification activities

During 1975–1976 the WHO Regional Office for Africa had medical epidemiologists stationed in Brazzaville (Dr Ziaul Islam), Côte d'Ivoire (Dr Alexander Dobrescu, Dr André Delas), and Nigeria (Dr Leva A. Arevshatian) to assist in epidemiological surveillance in western Africa. To coordinate the activities, Arita travelled throughout the area twice in 1975. During these trips a detailed manual describing how to carry out a pockmark survey was prepared and various technical and administrative problems were solved in discussions with the WHO epidemiologists and national health staff. At the request of WHO, Dr Joel G. Breman, at that time an epidemiologist from the United States Center for Disease Control working for the Organisation de Coordination et de Coopération pour la Lutte contre les Grandes Endémies en Afrique de l'Ouest (OCCGE), also assisted in promoting prep-

Table 25.9. Western Africa: number of reported cases of smallpox, 1966–1971

Country	1966	1967	1968	1969	1970	1971
Benin[a]	490	815	367	58	0	0
Côte d'Ivoire	10	2	0	0	0	0
Gambia	3	0	0	0	0	0
Ghana	13	114	24	0	0	0
Guinea	56	1 530	330	16	0	0
Guinea-Bissau[b]	0	0	0	0	0	0
Liberia	32	6	5	0	0	0
Mali	281	293	134	1	0	0
Mauritania	76	0	0	0	0	0
Niger	1 023	1 187	678	28	0	0
Nigeria	4 953	4 753	1 832	203	66	0
Senegal	0	0	0	0	0	0
Sierra Leone	293	1 697	1 143	80	0	0
Togo	201	332	784	83	0	0
Upper Volta[c]	69	195	100	0	0	0

[a] Formerly Dahomey.
[b] Portuguese Guinea until 1974.
[c] Now Burkina Faso.

arations in the OCCGE countries (Benin, Côte d'Ivoire, Mauritania, Niger, Senegal, Togo, and Upper Volta).

Preparation of country reports

In preparation for certification, each country was requested to provide, by the end of 1975, a formal country report documenting its smallpox eradication activities. Simple forms indicating the essential information required in the country report were distributed to all countries in the region in order to ensure uniformity in the documentation.

Pockmark surveys. Each of the countries was asked to organize pockmark surveys, carried out by special mobile teams operating for a period of 3–6 months. In order to simplify the operation, towns or villages with more than about 1000 inhabitants were to be selected, based on the demographic data for the country concerned, so that their combined population should be not less than 20% of the total population. In these localities, schools, maternal and child health clinics, hospitals and markets were to be visited to search for facial pockmarks in infants and children up to 15 years of age. Special instructions and forms describing how to select localities, how to conduct pockmark surveys and how to record the results were distributed to all the countries by WHO.

The surveys were completed by December 1975, and reports on the results became available in January 1976. As has already been mentioned, the localities surveyed were limited to large towns or villages, well distributed

Rationale for Pockmark Surveys in Western Africa

The rationale for conducting large-scale pockmark surveys in the countries of western Africa was outlined in 1976 in a memorandum by Henderson. In it, he discussed how best to provide the information that would allow an international commission to decide whether smallpox transmission had ceased in countries in which the last reported case had occurred several years earlier, and in which intensive smallpox surveillance had ceased some 5 years before the visit by the commission. He suggested that extensive facial pockmark surveys might be useful:

"For smallpox to have persisted during the past 4 years in the 15-country African area concerned, it is evident from what we know of the epidemiology of the disease that a large number of people living in a fairly large geographical area would have had to experience illness if the chain of transmission were to persist. Two-thirds of those afflicted would still bear facial scars of the disease and most of these would be children. To determine whether or not smallpox had been absent from this area, over this extended period, it would seem to me that one might examine a large number of children in many different geographical areas. If none had facial scars resembling those caused by smallpox which had been acquired during the past 4 years, one should be able to state with reasonable confidence that continuing smallpox transmission had not occurred in the 15-country area.

"To conduct such a study on a village-by-village basis would be ideal but expensive in terms of time and manpower. Practically, however, one might undertake to examine all those up to perhaps 15 years of age who attend school. Such an examination could be quickly performed as the children are already assembled in groups and children from a wide geographical area would be represented. Some, undoubtedly, would bear facial scars acquired more than 4 years before. If these children were identified, enumerated and the information confirmed that the disease had indeed been acquired more than 4 years previously, this would be further evidence that facial scars would be identified if present.

"An assessment which would be much simpler than this would be hard to visualize. The difficulties in undertaking such an appraisal would need to be carefully considered and, as well, whether the evidence obtained (with such other data as might be compiled) would be sufficient to permit an international commission to endorse the view that smallpox had been eliminated from the 15-country area concerned."

throughout the country; small villages in remote and inaccessible areas were excluded because of the considerable time and resources that would have been required to reach them. The view was taken, and later accepted by the International Commission, that, if smallpox transmission had continued, the disease should have reached larger towns or villages at some time between 1971 and 1976, and pockmarked persons would have been seen there.

The selection of localities can be illustrated by the arrangements made in Nigeria, the largest and most populous country in the region and the major focus of smallpox during the eradication campaign (see Chapter 17). Table 25.10 shows the numbers of localities of various sizes selected for assessment and their total population; 9.5% of all inhabited localities were surveyed, accounting for 37.7% of the total population of Nigeria. The localities were widely scattered throughout the country; their geographical distribution is shown in Fig. 25.6.

The field survey teams in the 15 countries examined a total of 6.5 million persons, made up of 1.6 million preschool children, 3.7 million primary-school children and 1.2 million over primary-school age, representing over 25% of schoolchildren up to 13 years of age and 5% of the total population of 122.4 million of western Africa (Table 25.11).

Table 25.10. Nigeria: number of localities selected for facial pockmark surveys, by population size

Population size of locality	Number of localities	Total population of localities
⩾ 10 000	664	22 115 000
8 000–9 999	132	1 188 000
6 000–7 999	242	1 694 000
4 000–5 999	221	1 105 000
2 000–3 999	470	1 410 000
< 1 000–1 999	88	88 000
Total	1 817	27 600 000

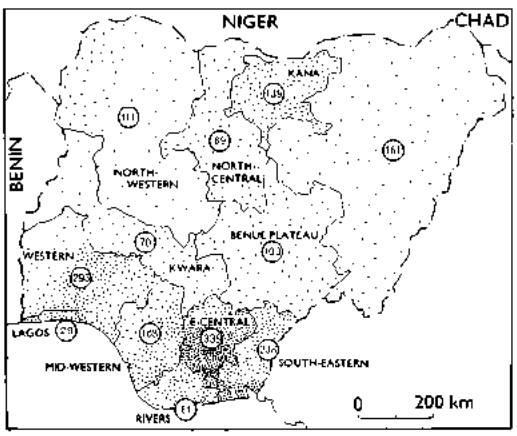

Fig. 25.6. Geographical distribution of the 1817 localities in Nigeria in which facial pockmark surveys were conducted during 1975.

Table 25.11. Western Africa: results of facial pockmark surveys carried out in 1975–1976

Country	Population (millions)[a]	Number of persons examined			
		Total	Preschool age[b]	Primary-school age[b]	Over primary-school age[b]
Benin[c]	3.0	188 722	12 881 (0)	175 841 (208)	0
Côte d'Ivoire	6.7	236 194	960 (0)	235 234 (144)	0
Gambia	0.5	24 694	2 481 (0)	11 207 (8)	11 006 (33)
Ghana	9.8	724 465	30 074 (0)	454 215 (5)	240 176 (56)
Guinea	4.3	68 263	0	68 263 (546)	0
Guinea-Bissau	0.6	28 156	1 463 (0)	26 408 (0)	285 (2)
Liberia	1.6	77 717	4 316 (0)	34 545 (5)	38 856 (31)
Mali	6.3	412 271	76 735 (0)	246 087 (75)	89 449 (93)
Mauritania	1.4	63 382	19 665 (0)	43 717 (0)	0
Niger	4.7	49 990	1 384 (0)	44 794 (71)	3 812 (5)
Nigeria	67.7	3 840 828	1 387 227 (0)	1 860 563 (2 923)	593 038 (3 789)
Senegal	4.8	257 388	2 639 (0)	82 223 (61)	172 526 (113)
Sierra Leone	3.1	230 437	68 079 (0)	162 358 (104)	0
Togo	2.3	177 221	0	177 221 (59)	0
Upper Volta[d]	5.6	117 522	24 014 (0)	74 256 (13)	19 252 (46)
Total	122.4	6 497 250	1 631 918 (0)	3 696 932 (4 222)	1 168 400 (4 168)

[a] Population data for 1975 from United Nations (1985).
[b] Number of persons with facial pockmarks shown in parentheses.
[c] Formerly Dahomey.
[d] Now Burkina Faso.

During these surveys, over 8000 individuals with facial pockmarks were identified among persons of primary-school age or older. Almost all of them had had smallpox before 1971; in a few, the lesions were due to other causes. In no case did the interrogation reveal a missed case of smallpox. There were no pockmarks among children below the age of 6 years.

Suspected smallpox cases. During the pockmark surveys the teams visited hospitals and dispensaries to ascertain whether there were any rumours of smallpox. If suspected cases were seen, specimens were taken for laboratory examination.

Between 1972 and 1976, 11 countries in the region had reported 127 cases of suspected smallpox, none of which was confirmed on investigation. In contrast to the extensive laboratory investigations in Indonesia (see Table 25.8), between 1971 and 1973, only 75 laboratory specimens had been sent to the WHO collaborating centre in Atlanta, USA, from western Africa (Table 25.12), because no special searches for suspected smallpox had been carried out. None of these specimens yielded variola virus, but in 41 of them herpesvirus particles were seen by electron microscopy.

Table 25.12. Western Africa: results of laboratory investigation of suspected cases of smallpox by the WHO collaborating centre, Atlanta, USA, January 1972–April 1976[a]

Country	Number of specimens	Herpesvirus particles seen	Vaccinia virus isolated	Negative
Benin[b]	1	1	0	0
Côte d'Ivoire	12	10	0	2
Gambia	0	0	0	0
Ghana	8	5	0	3
Guinea	0	0	0	0
Guinea-Bissau[c]	0	0	0	0
Liberia	5	2	0	3
Mali	0	0	0	0
Mauritania	1	1	0	0
Niger	5	3	0	2
Nigeria	31	12	2	17
Senegal	0	0	0	0
Sierra Leone	4	2	0	2
Togo	0	0	0	0
Upper Volta[d]	8	5	0	3
Total	75	41	2	32

[a] In no case was variola virus recovered.
[b] Formerly Dahomey.
[c] A Portuguese colony until 1974.
[d] Now Burkina Faso.

Visit of the International Commission

The International Commission met first in Abidjan, Côte d'Ivoire, from 23 to 26 March 1976, to review the country reports and survey data. Western Africa was divided into 5 zones, each of which was visited by a team consisting of members of the International Commission accompanied by temporary advisers and WHO personnel. Each team visited all the countries in the zone allocated to it. Their investigations included a review of additional records available at the national and local levels, interviews with personnel involved in various aspects of the programme, and visits to selected localities to verify the sensitivity and effectiveness of the smallpox surveillance effort, including verification of the recently completed facial pockmark surveys. The Commission finally met in Brazzaville from 12 to 15 April to consider the additional data obtained during the field visits.

A number of questions had been clarified during the field visits. Overall, the reports showed that in all the countries excellent vaccination and surveillance programmes had been conducted in 1967–1972 and good pockmark surveys in 1975. Although the surveillance and reporting systems in most countries were better than those in operation before the eradication programme began in 1967, no cases of smallpox had been reported from any country in the region since 1970. In addition, between 1970 and 1976, 8 cases of human monkeypox had been discovered in Côte d'Ivoire, Liberia, Nigeria and Sierra Leone. The disease resembled smallpox clinically but not in its epidemiology (see Chapter 29). The fact that these cases, which had occurred in remote areas, had been discovered was evidence of the efficiency of the surveillance systems.

The long period (6 years) of apparent freedom from smallpox in western Africa predisposed the Commission to believe that transmission had been interrupted, a view that was strongly supported by the fact that the very extensive pockmark survey had produced no evidence of smallpox transmission after 1971.

The Commission concluded that there was no evidence that smallpox had occurred in the 15 countries of western Africa since 1970, and certified the region as being free of smallpox. Bearing in mind that smallpox transmission persisted in Ethiopia, however, it recom-

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Plate 25.2. Participants in the meeting of the International Commission for the Certification of Smallpox Eradication in Western Africa, 15 April 1976. *Left to right, front row:* **W. Koinange (Kenya), I.D. Ladnyi (USSR), P.F. Wehrle (USA), Lekie Botee (Zaire), S. Bédaya-Ngaro (Central African Republic), M.I.D. Sharma (India), R. Netter (France)**; *back row:* C. Algan (WHO), J.G. Breman (USA), A.N. Slepushkin (WHO), B. Guyer (USA), A. Dobrescu (WHO), E.A. Smith (Nigeria), D.A. Henderson (WHO), C.R. Jones (WHO), Z. Islam (WHO), A.K. M'Baye (Senegal), J.A. Mahoney (WHO), A.E. Delas (WHO), A.H. Abou-Gareeb (WHO), F.C. Grant (Ghana), I. Arita (WHO). The names of the Commission members are in bold type.

I.D. LADNYI

Plate 25.3. Checking schoolchildren in Nigeria for vaccination scars and facial pockmarks during the visit of the International Commission to western Africa, March 1976.

Table 25.13. Central Africa: number of reported cases of smallpox, 1965–1972

Country	1965	1966	1967	1968	1969	1970	1971	1972
Burundi	1 213	363	74	301	108	197	0	0
Cameroon	28	2	119	37	3	0	0	0
Central African Republic	0	0	0	0	0	0	0	0
Chad	73	0	86	5	0	0	0	0
Congo	89	0	0	0	0	0	0	0
Equatorial Guinea	0	0	0	0	0	0	0	0
Gabon	1	0	0	0	0	0	0	0
Rwanda	5	0	0	0	107	253	0	0
Zaire	3 783	1 913	1 479	3 800	2 072	716	63	0

mended that vaccination programmes should continue, particularly for preschool children. Continued careful surveillance, and especially the reporting and investigation of all chickenpox outbreaks in which deaths had occurred, was most important, so as to make certain that these outbreaks were not caused by smallpox introduced from an endemic area or by monkeypox or related viruses.

CENTRAL AFRICA

Following the certification of smallpox eradication in the 15 countries of western Africa, preparations for certification were organized over the period June 1976 to June 1977 for 9 countries of central Africa: Burundi, Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Rwanda and Zaire (Fig. 25.7). Apart from forming a geographical unit, these countries shared several features which made it reasonable to group them together for certification. As in western Africa, the USA had supported a smallpox eradication and measles control programme in certain countries in the region between 1967 and 1972—namely, Cameroon, the Central African Republic, Chad, the Congo, Equatorial Guinea and Gabon. WHO-assisted smallpox eradication programmes had been in operation in Burundi, Rwanda and Zaire. Zaire, the largest of these 9 countries, with a population of 26 million in 1977 (half the entire population of the group), developed a WHO-assisted smallpox eradication programme in 1967. The last case of smallpox in Zaire—the last in this group of countries—was recorded in June 1971, and active surveillance was continued throughout Zaire, with WHO support, until 1977.

Fig. 25.7. The 9 countries of central Africa certified free of endemic smallpox by the International Commission in June 1977.

French was the official language of 8 of these central African countries,[1] making it much easier to prepare documentation and arrange meetings than in western Africa, in which both English and French had to be used.

Recent History of Smallpox

Smallpox had been endemic in most of these countries until the mid-1960s (Table 25.13). In the 1950s and early 1960s outbreaks

[1] Both English and French are official languages in Cameroon, while Spanish is that of Equatorial Guinea.

of both variola major and variola minor had been reported in Zaire, but there was some uncertainty about the validity of diagnoses (see Chapter 18). After 1962 the usual African type of variola major was the only variety of smallpox seen in all these countries, hence pockmark surveys promised to be as useful here as they had proved to be in western Africa.

Preparations for Certification

Coordination of precertification activities

It had been agreed that, in preparing for certification, activities similar to those found satisfactory in western Africa should be carried out—namely, the preparation of standardized, relatively simple country reports and the organization of pockmark surveys. Work on the preparation of country reports was begun in July 1976, and from 11 to 15 October 1976 a coordination meeting was held in Brazzaville to discuss the preliminary results and the procedures to be followed.

Representatives from the 9 countries, together with consultants and staff from the WHO Smallpox Eradication unit, attended the meeting, at which the preliminary country reports submitted by country representatives and the methodology of pockmark surveys were reviewed. WHO agreed to provide funds to cover the local travelling expenses (living allowances, petrol and oil) of mobile teams carrying out pockmark surveys. June 1977 was agreed as the date for the visit of the International Commission, since it was thought that by then all country reports and pockmark surveys would have been completed.

Dr Islam provided each country with the statistical data available at the WHO Regional Office for Africa in Brazzaville. Since such data were not always easily available in the countries concerned, this greatly facilitated the preparation of the country reports.

Zaire was treated differently from the other countries. A detailed country report was requested, but it was agreed that pockmark surveys would be carried out only in the epidemiologically critical border areas, since country-wide active surveillance for smallpox had continued ever since the discovery of the last case in 1971. A special monkeypox survey was planned as part of the precertification activities, since monkeypox was clinically indistinguishable from smallpox. It consisted of a search for unreported human monkeypox cases or smallpox-like disease in areas within a 25-kilometre radius of villages in which human monkeypox cases had occurred in the past.

Preparation of the country reports

Pockmark surveys. The field survey teams examined over 1.3 million persons, constituting 2.5% of the total population of the central African countries (Table 25.14). In all, 1.5% of preschool children and 8.8% of schoolchildren were examined. Pockmarks were found in 1420 schoolchildren and 146 adults, but there were none in the preschool age group (0–5 years).

Table 25.14. Central Africa: results of pockmark surveys, 1976–1977

Country	Population (millions)[a]	Number of persons examined			
		Total	Preschool age[b]	School age[b]	Adults[b]
Burundi	3.9	77 574	6 000 (0)	71 574 (18)	0
Cameroon	7.9	326 819	14 428 (0)	312 391 (6)	0
Central African Republic	2.1	119 277	17 920 (0)	101 357 (0)	0
Chad	4.2	158 849	13 802 (0)	130 806 (78)	14 241 (1)
Congo	1.4	93 162	7 440 (0)	80 935 (19)	4 787 (0)
Equatorial Guinea	0.3	8 942	353 (0)	8 589 (0)	0
Gabon	1.0	71 331	5 298 (0)	66 033 (55)	..[c] (1)
Rwanda	4.7	81 149	9 109 (0)	72 040 (6)	0
Zaire	26.2	396 440	48 491 (0)	264 738 (1 238)	83 211 (144)
Total	51.7	1 333 543	122 841 (0)	1 108 463 (1 420)	102 239 (146)

[a] Population data for 1977 from United Nations (1985).
[b] Number of persons with facial pockmarks shown in parentheses.
[c] . . = data not recorded.

Laboratory diagnosis. The number of specimens sent to WHO collaborating centres between 1972 and 1976 varied from one country to another (Table 25.15), but the great majority were collected in Zaire. Variola virus was not found in any of the 748 specimens examined, but 14 specimens collected in Zaire were found to contain monkeypox virus.

Visit of the International Commission

The first meeting of the Commission was held in Brazzaville from 6 to 8 June 1977. Subsequently, the Commission formed 6 teams, which between them visited all the countries in the region. The type of investigation undertaken by these teams can be illustrated by the report of the subgroup that visited Zaire, which consisted of Dr A. M'Baye and Dr J. G. Breman, Commission members from Senegal and the USA respectively, assisted by Dr Pierre Ziegler and Dr Edilberto Zanotto, former WHO staff from the Zaire smallpox eradication programme.

Between 8 and 26 June 1977 the subgroup reviewed the country report, the results of the facial pockmark survey and the special report on monkeypox, and visited 28 zones in Zaire, including some in each of the 9 regions of the country. In addition, the detailed locally prepared survey reports were reviewed and 57 government and private health units visited.

The subgroup also visited 35 schools, 16 markets and a refugee camp in order to examine preschool children and schoolchildren for facial pockmarks caused by smallpox. In all, 13 450 children were examined or re-examined. No child of less than 7 years of age showed facial pockmarks attributable to smallpox. The vaccination coverage of schoolchildren was satisfactory (about 90%). Investigations by national staff of 33 suspected cases were reviewed by the subgroup; no evidence of recent smallpox was found.

The Commission met again in Brazzaville from 28 to 30 June 1977 and, after discussing the findings of the field visits, concluded that there was no evidence that smallpox had occurred in any of the 9 countries of central Africa since August 1971. Specific questions by the teams about variolation and laboratory stocks of variola virus elicited the information that variolation was not practised in any of these countries, nor were stocks of variola virus held in their laboratories. Since smallpox was still endemic in Somalia, the Commission recommended that careful surveillance should be continued and vaccination campaigns maintained, particularly for preschool children, in all countries until such time as the global eradication of smallpox could be certified. The Commission also recommended that active surveillance of human monkeypox should be maintained.

Table 25.15. Central Africa: number of specimens from suspected cases of smallpox submitted to WHO collaborating centres for laboratory diagnosis, 1972–1976

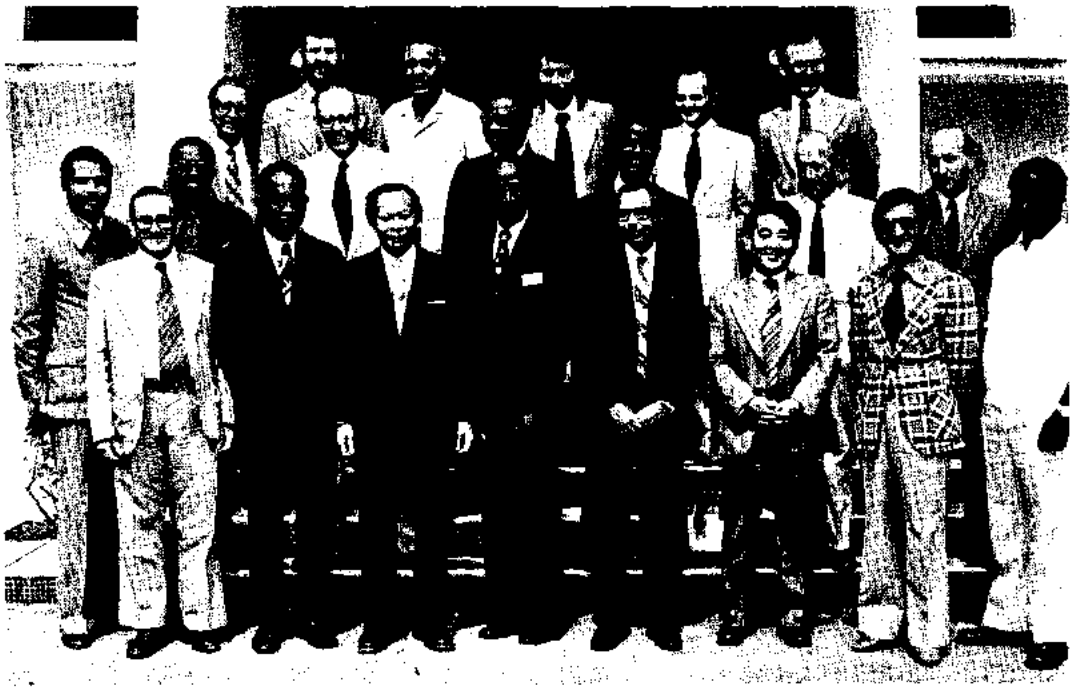
Country	Number of specimens[a]	Monkeypox virus present
Burundi	1	0
Cameroon	18	0
Central African Republic	16	0
Chad	11	0
Congo	3	0
Equatorial Guinea	0	0
Gabon	6	0
Rwanda	2	0
Zaire	691	14
Total	748	14

[a] All negative for variola virus.

CERTIFICATION IN AFGHANISTAN AND PAKISTAN

Afghanistan and Pakistan, which share a border of about 1000 kilometres, were the first countries on the Asian mainland from which the eradication of smallpox was certified. In both, the national eradication programmes were started in 1967; the last cases were recorded in 1973 and 1974 respectively. The geographical features and ethnic make-up of the border areas were similar on both sides of the frontier and cases had been imported across it into Afghanistan. Smallpox was still endemic in India in 1975, but Pakistan's long border with India was closed, and population movements across it were infrequent.

In contrast to the situation in western and central Africa, in which the last outbreaks occurred in 1970 and 1971 respectively and many countries in both regions had been free of endemic smallpox for several years previously, the disease had been endemic in Afghanistan and Pakistan recently enough for the intensified surveillance of the later



WHO / R. C. DA SILVA

Plate 25.4. Participants in the meeting of the International Commission for the Certification of Smallpox Eradication in Central Africa, 30 June 1977. *Left to right, front row:* M. Altmann (WHO), **P. Agbodjan (Togo)**, Le Van Giat (WHO), **A.K. M'Baye (Senegal)**, Z. Islam (WHO), I. Arita (WHO), C. Algan (WHO), Kalisa Ruti (Zaire); *middle row:* R. Molouba (Congo), J.A. Mahoney (WHO), P. Ziegler (WHO), **M. Yekpé (Benin)**, **E. Coffi (Côte d'Ivoire)**, **F. Dekking (Netherlands)**, E. Zanotto (WHO); *back row:* A.H. Abou-Gareeb (WHO), **J.G. Breman (USA)**, A.W. Wilson (WHO), J.-P. Jardel (WHO), **R. Netter (France)**, J.J. Rogowski (WHO). The names of the Commission members are in bold type.

stages of the eradication programme to be carried over into the preparations for certification. For this reason reliance was placed on active surveillance and searches, rather than on the pockmark surveys used in Africa. The same international commission dealt with the certification in both countries in the latter part of 1976, a few months after the certification of western Africa and before that of central Africa.

AFGHANISTAN

The last case in Afghanistan was recorded in July 1973 but, because of the prevalence of smallpox in neighbouring Pakistan and the concern that foci of unreported smallpox might remain in remote areas of the country, surveillance was reinforced. Dr Arcot G. Rangaraj, a WHO epidemiologist, remained in Afghanistan until certification had been completed. Dr Abdul Mohammad Darmanger of the Ministry of Health played an important role in the 12-member National Committee for Smallpox Eradication, which took responsibility for the preparations for certification.

Analysis of the sources of outbreaks occurring during the last 4 years of endemic smallpox (Table 25.16) showed the need to pay particular attention, in the precertification surveillance activities, to variolation and nomadic groups.

Precertification Activities

Surveillance: 1973–1975

For operational purposes, Afghanistan was divided into 4 zones (see Chapter 14, Fig. 14.3) and subsequently into 3 zones—namely, Kabul, Kandahar and Kunduz (see Fig. 25.8). To search for and investigate suspected cases, special surveillance teams had continued work after the last case, 3 teams being located in the Kabul zone, 3 in the Kandahar zone, and 1 in the Kunduz zone. Special surveys

Table 25.16. Afghanistan: outbreaks of smallpox, 1970–1973

Source of outbreaks	1970		1971		1972		1973	
	Number	%	Number	%	Number	%	Number	%
Importations from Pakistan	11	13	13	12	18	41	3	100
Variolation	23	27	21	19	3	7	0	–
Nomads	8	10	4	4	5	11	0	–
Hospitals	5	6	2	2	0	–	0	–
Kabul city	8	10	4	4	0	–	0	–
Other endemic foci	8	10	51	48	14	32	0	–
Undetermined	20	24	12	11	4	9	0	–
Total number of outbreaks	83		107		44		3	
Total number of cases	1 044		736		236		25	

were organized in areas in which smallpox outbreaks had occurred after 1967, either through natural transmission or through variolation, and in border provinces, as well as those in which nomads were concentrated during the summer. During the period 1974–1975, 255 of the 327 administrative units of the country (78%) were visited by surveillance teams, but no new focus of smallpox infection, indigenous or imported, was detected.

About 700 villages were identified in which variolation had been practised in the past, and 90 of them—those in which it had been performed most recently—were repeatedly checked and visited. Neither practising variolators nor fresh variolation scars were detected. In addition, 155 nomad encampments were visited and searched in the Kabul, Kunduz and Kandahar zones, with the same result.

Special active search in 1976

A special active search for suspected cases in rural areas was carried out in 1976 by 7 smallpox surveillance teams and 15 combined BCG/smallpox vaccination teams. These teams checked all villages with more than 250 persons and, regardless of the size of the population, all previously affected villages and those in which variolation had been practised. The teams moved from province to province, arranging their operations according to the climatic and geographical conditions of the area to be searched. Of the 28 provinces, 22 were covered, an average of 6–8 villages being visited daily by each team. Over 8000 villages were searched, accounting for 93% of the villages with a population of more than 250 in the country. Teams also visited and interviewed people in 1548 markets, 2100 tea-shops and 1192 schools throughout the country. Two months later, the same areas were visited by assessment teams which interviewed villagers and assessed the work of the search teams in 10% of these villages. It was found that many villagers had seen searchers and 88% knew where and to whom to report suspected cases. During the search, 262 suspected cases of smallpox were found; 135 (51%) of them proved to be cases of chickenpox and 110 (42%) measles; the remaining 17 were cases of other skin diseases such as eczema, scabies and dermatitis.

A special pockmark survey was conducted among the 0–4-year-old children of nomads. Altogether, 5107 of these children were examined in 8 provinces inhabited by nomads during the summer. Only 2 children with pockmarks were found, both of whom had contracted smallpox more than 3 years earlier while travelling between Pakistan and Afghanistan.

Collaboration of the malaria control programme in the active search

During the period April–June 1976, in addition to the active searches carried out by surveillance and mobile vaccination teams, about 1000 malaria control programme workers carried out another search in densely populated areas below an elevation of 2000 metres—i.e., where malaria transmission occurred. About 13 000 villages were visited, 680 000 households searched and about 3 million people interviewed. Not only were suspicious cases detected, none of which proved to be smallpox, but the search also assisted in increasing the awareness of the

population of the need to notify suspected smallpox cases.

Hospital searches

In April June 1976, local health staff in provincial hospitals, maternal and child health clinics and basic health centres made inquiries among visiting outpatients about any suspected cases present in their home villages or towns. The search resulted in the detection of 223 suspected cases; 55% proved to be measles and 28% chickenpox, the remaining 17% including a variety of skin diseases. Furthermore, staff of the provincial hospitals participated in searches in the towns and in villages located within a 5-kilometre radius. As an incentive, from 1976 onwards a reward of 3000 afghanis (US$51) was offered for every report of a confirmed case of smallpox. Despite these activities, no evidence was found of recent smallpox. All the results indicated that smallpox had not been present in the country during the previous 3 years.

Variolation

From the inception of the Intensified Smallpox Eradication Programme in Afghanistan, there was concern that variolators, who were especially active in the central and eastern parts of the country, might play an important role in smallpox transmission (see Chapter 14). In fact, 47 of the 237 outbreaks recorded between 1970 and 1973 could be specifically attributed to variolation (see Table 25.16). The last known variolation in Afghanistan was recorded in Dand Area of Kandahar Province in April 1976. However, none of the 57 children variolated at that time had developed any skin lesions at all. Evidently the variolation material used contained no viable virus.

Throughout the eradication programme, staff had attempted to identify variolators, to learn about their practices, and to persuade them to give up variolation. Whenever possible, they collected specimens of variolation material so that it could be assayed for the presence of viable virus. Also, intensive efforts were made to educate the population about the dangers of variolation and to vaccinate systematically throughout the country in order to demonstrate that vaccination was available to all. These measures proved to be remarkably successful.

The remaining question of concern was whether it might be possible for a variolator to retain over a period of many years scabs containing viable variola virus of sufficiently high titre to permit successful variolation. Variolators who were interviewed in 1976 claimed to have given up the practice during the previous few years, partly because villagers had gradually ceased to seek their services and partly because of pressure from the government. Most variolators asserted that the variolation material they had used was not effective for more than 1 or, at most, 2 years. Since smallpox had been absent from the country during the past 2 years it was therefore thought unlikely that many persons would attempt variolation because of the lack of effective material. Of 9 specimens collected from variolators in Afghanistan from 1969 to 1976, none had yielded viable virus since 1970, when smallpox was still endemic (Table 25.17).

Specimens were studied by virus isolation and electron microscopy, virus being isolated

Table 25.17. Afghanistan: results of laboratory tests of specimens of variolation material obtained from variolators

Age of specimen	Type of material	Date collected	Results	
			Poxvirus particles by electron microscopy[a]	Virus isolation
?	Fluid	March 1969	..	+
9 months	Scabs	May 1969	..	+
4 months	Scabs	September 1969	..	+
?	Scabs	April 1970	..	+
?	Scabs	January 1972	−	−
?	Scabs	April 1976	+	−
6 years	Powder	May 1976	+	−
6 years	Scabs	May 1976	+	−
10 years	Scabs	May 1976	+	−

[a] Virus particles may be visualized by electron microscopy, even though not viable; .. = not done.

from 4 of them. Three of the isolations were made from relatively fresh samples, 2 being between 4 and 9 months old; the third was fluid and would have dried up if it had been stored for more than 12 months. The fact that, as Table 25.17 shows, in 4 other specimens numerous poxvirus particles could be demonstrated by electron microscopic examination but virus could not be isolated suggested that viable variola virus probably did not survive under normal conditions for more than 2 years, or perhaps a much shorter period.

However, in the cold mountainous regions of Afghanistan in particular, the possibility could not entirely be ignored that one or more variolators might have been able to preserve for years material which contained variola virus with a titre sufficient to produce successful takes. One variolator from Kunar Province had stated in an interview that he (as well as a colleague in Peshawar, Pakistan) usually preserved scabs in a screw-capped container which was buried in the ground in a mountainous area. He considered this material to be effective for up to 10 years. On further questioning, however, he stated that fresh material had to be added to the basic stock each year.

Visit of the International Commission

The International Commission visited Afghanistan between 22 and 29 November 1976. After a preliminary meeting in Kabul, members of the Commission visited the 3 national smallpox eradication programme zones (Fig. 25.8) before their final meeting in Kabul.

They found that good records had been kept of smallpox control activities and that the work of the zonal smallpox eradication programme staff was of a high order. The basic health service units played a valuable role in investigating suspected cases of smallpox, but the recording and reporting of such activities was not standardized and was deficient in places. A number of recent suspected cases were reinvestigated and confirmed not to have been smallpox. The pockmark surveys of children showed that no outbreaks had occurred after the time when the zone concerned had been considered to be free from smallpox. No pockmarks were observed in children under the age of 5 years.

Checks for vaccination scars confirmed that a very high proportion of children had been vaccinated, as reported by national smallpox eradication programme staff, the major exceptions being in some nomad camps, where small groups of families were found to have been missed. The Commission teams were most impressed with the level of knowledge about smallpox, vaccination and the importance of reporting suspected cases found among all sections of the community. Knowledge of the reward was widespread in most of the provinces visited.

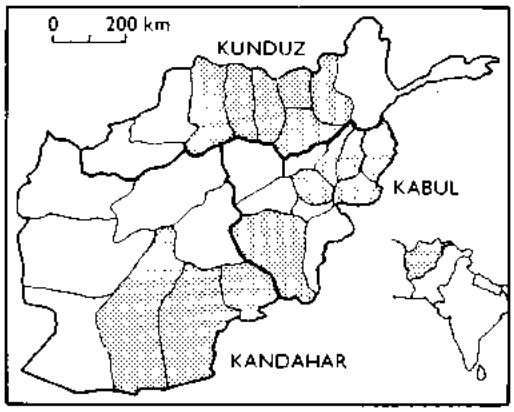


Fig. 25.8. Provinces (shaded) in the 3 zones of Afghanistan visited by members of the International Commission in November 1976.

Variolation scars, which could be distinguished from scars due to vaccination since they were on the wrists or the dorsum of the forearm (see Chapter 14), were common in adults, but there was no evidence of recent variolation other than that reported in Kandahar Province in April 1976, already mentioned.

The Commission certified smallpox eradication in Afghanistan on 30 November 1976, noting that the energetic and thorough surveillance activities carried out since 1972 would have been adequate to disclose cases of smallpox if they had occurred. Because some parts of Asia had still to be certified and the transmission of smallpox was still occurring in the Horn of Africa, the Commission recommended that surveillance and vaccination should be continued until global eradication had been certified.

As far as variolation was concerned, the Commission concluded that, although it was unlikely that scabs containing live virus remained in the possession of variolators, the possibility that variolation might cause future outbreaks could not be completely

excluded. The Commission was concerned about this prospect and strongly recommended that vigilance should be maintained. In fact, a further 3 years elapsed after the Commission's visit before the Global Commission finalized its report, during which time no case of smallpox was reported. This strengthened the belief that viable variola virus did not survive in variolators' material.

PAKISTAN

The last case of smallpox occurred in Pakistan in September 1974 (Table 25.18) and eradication was certified in December 1976.

Precertification Activities

As in Afghanistan, surveillance measures were further strengthened in all provinces after eradication because of the concern that foci of unreported cases might still be present, especially in "problem areas"—i.e., areas not easily accessible for geographical or political reasons. First priority was given to active search operations.

Country-wide searches

In 1975 several active searches were carried out by various categories of staff: vaccinators, searchers, malaria and family planning field staff and other health workers. In 1976 the searches were extended to the entire country, covering the majority of the rural areas. Three complete search operations were carried out in January, May and August 1975, usually for periods of 2 weeks each, although this was extended to 21 working days in many areas to ensure the best results. After each search operation, an independent assessment was made by the district and provincial surveillance teams, covering 5% of randomly selected localities in the territory already searched.

Similar search operations were carried out in urban areas throughout Pakistan. The administrative organization and health services available in the towns made it necessary for these searches to be carried out independently of those in rural areas. In general, municipal vaccinators and general health staff, supported by volunteers, carried out house-to-house searches in all slums, sweeper colonies (areas to which migrants normally went), other poor socio-economic areas, cantonment areas, railway settlements, the areas in which the last 20 outbreaks of smallpox had occurred, and the areas on the outskirts of towns in which nomads usually settled. In June and July 1976 a special all-Pakistan urban search was carried out in towns with a population of over 50 000, and in all district headquarter towns, regardless of their size. An intensified health education campaign was also carried out in these towns before search activities commenced.

Searches in problem areas

Provincial and district surveillance teams, assisted by local health staff, organized repeated special searches in the problem areas previously mentioned, which might not have been properly searched in the course of eradication activities. As a rule, randomly selected villages and settlements in such areas were visited, and information on the occurrence of smallpox cases during the past 2 years was collected and checked; in addition, vaccination scar and pockmark surveys were carried out among children under 5 years of age.

These special searches were intensified during the first half of 1976, when particular attention was paid to parts of Azad Kashmir, the areas bordering on China, remote areas of Baluchistan inhabited by nomads, mountain-

Table 25.18. Pakistan: number of reported cases of smallpox, 1970–75, by province or area

Province or area	1970	1971	1972	1973	1974	1975
Azad Kashmir	0	0	0	0	9	0
Baluchistan	80	291	559	801	202	0
North-west Frontier	525	2 654	1 338	194	163	0
Punjab	1 480	2 036	1 495	415	1 503	0
Sind	1 107	827	3 661	7 848	5 982	0
Total	3 192	5 808	7 053	9 258	7 859	0

ous parts of Punjab, flood-affected riverine areas in Sind and on the border with India, and the Thar desert (Fig. 25.9).

Active searches in areas in which the last outbreaks occurred

During 1975 and again in March–April 1976, a special team composed of the most competent vaccinators, sanitary inspectors and health assistants, together with district surveillance teams, visited the areas in which the last 20 outbreaks had occurred in each district, reassessed the previous reporting, case-finding and containment activities, and carried out an active case search in all the localities within a 5-mile (8-kilometre) radius of the previously affected areas. Pockmark surveys were conducted on a large scale, particularly among children under 2 years of age, in an effort to find undisclosed cases, but none was found in that age group.

In the districts in which smallpox incidence had been low and the number of outbreaks small, all localities which had had smallpox outbreaks in 1974 were visited and the epidemiological situation rechecked in an effort to disclose possible continuing transmission.

To assess surveillance independently, surveillance teams from one province visited another province or area for periods varying from a few weeks to 2 months. Thus, in 1976, provincial and district teams from Punjab assessed the efficacy of the programme operations in Azad Kashmir, Baluchistan, and North-west Frontier Province; Sind provincial and district teams did the same in Baluchistan and Punjab.

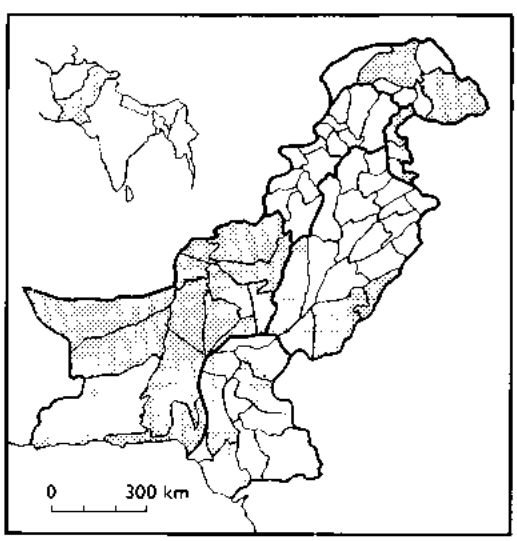


Fig. 25.9. "Problem areas" in Pakistan (shaded), in which special searches were carried out during pre-certification activities in 1976.

Rewards

The cash reward offered for finding smallpox cases was increased from 100 rupees (US$10) to 200 rupees, and in July 1975 to 500 rupees. The reward was publicized as widely as possible by means of the radio, press and wall posters in order to encourage the public to report suspected cases.

In November 1975, the following new system of rewards was introduced:

— 1000 rupees to anyone who reported an active case of smallpox;

— 100 rupees to any health worker who discovered a child with facial pockmarks that originated from a smallpox-like disease which had occurred after October 1974;

— 1 rupee to search workers for every chickenpox case visited and recorded during the all-Pakistan search operation in January 1976.

The participation of the local administrative authorities was sought. A special postcard, signed by the Deputy Commissioner, was sent to each *numberdar* (village leader), asking him to question, within a week, all the inhabitants of his village as to the presence of smallpox cases and, if any existed, to report them immediately to the district authorities.

Results

As a result of all these activities, 49 874 cases of fever with rash were detected, reported and investigated by November 1976. The reporting of cases of chickenpox during the search periods was encouraged (Table 25.19), on the assumption that a surveillance system sufficiently sensitive to detect them would almost certainly detect smallpox outbreaks. Altogether, 27 703 chickenpox cases were reported. Laboratory specimens were collected from 157 cases in which the diagnosis was in doubt and tested by WHO collaborating centres for the presence of variola virus, with negative results. No focus of smallpox infection, indigenous or imported, nor any recent case of smallpox was detected. All the information obtained in

Table 25.19. Pakistan: number of cases of fever with rash investigated and number of cases of chickenpox reported between October 1974 and September 1976, by province or area

Province or area	Number of cases of fever with rash	Number of cases of chickenpox
Azad Kashmir and northern areas	608	524
Baluchistan	242	184
North-west Frontier	6 878	3 196
Punjab	31 267	16 658
Sind	10 979	7 141
Total	49 874	27 703

1975–1976 served to confirm that the disease had not been present in the country since October 1974.

Variolation

Variolation had been practised in Pakistan both in North-west Frontier Province and to a lesser extent in Punjab, but on nothing like the scale found in Afghanistan. Material was collected from several variolators during 1975. In 1976, local health staff throughout the country were asked to inquire about variolations performed in the last 12–18 months, to visit the areas concerned, and to try to locate the variolators and collect variolation material from them. Examination of 11 specimens by electron microscopy revealed poxvirus particles in 9, none of which yielded viable virus (Table 25.20). One specimen collected in 1975 showed numerous herpesvirus particles, suggesting that a professional variolator, desperate to find a smallpox patient from whom he could replenish his material, took specimens from a chickenpox patient, either deliberately or after misdiagnosis.

Visit of the International Commission

The International Commission for the Certification of Smallpox Eradication in Afghanistan was also responsible for certification in Pakistan. It travelled to Islamabad after completing its visit to Afghanistan, and remained in Pakistan from 6 to 18 December 1976, members visiting 37 of the 71 districts or agencies in the country (Fig. 25.10).

Field visits

Evidence of the recent occurrence of smallpox was sought by means of pockmark surveys, especially among children, and by questioning people. A number of recent suspected cases were reinvestigated and confirmed not to have been smallpox. The areas selected for special searches included some of those in which smallpox had occurred late in 1974. Scar surveys were carried out to assess vaccination coverage and the extent of variolation. Where possible, known variolators were traced and interviewed and sites of outbreaks due to variolation were revisited. Inquiries were made among different sections of the population to determine the extent of

Table 25.20. Pakistan: results of laboratory tests of specimens of variolation material obtained from variolators

Province	Age of specimen (years)	Type of material	Date collected	Results	
				Electron microscopy[a]	Virus isolation
North-west Frontier	3–6	Scabs	March 1976	+	–
	4–5	Scabs	April 1976	+	–
	3–8	Scabs	April 1976	+	–
	4	Scabs	May 1976	+	–
	3	Scabs	July 1976	+	–
	?	Scabs	August 1976	+	–
	?	Scabs	August 1976	+	–
Punjab	1	Scabs	March 1975	[b]	–
	4	Scabs	April 1975	+	–
	2	Scabs	May 1975	+	–
	?	Scabs	May 1975	[c]	–

[a] + = orthopoxvirus particles seen.
[b] Not done.
[c] Herpesvirus particles seen.

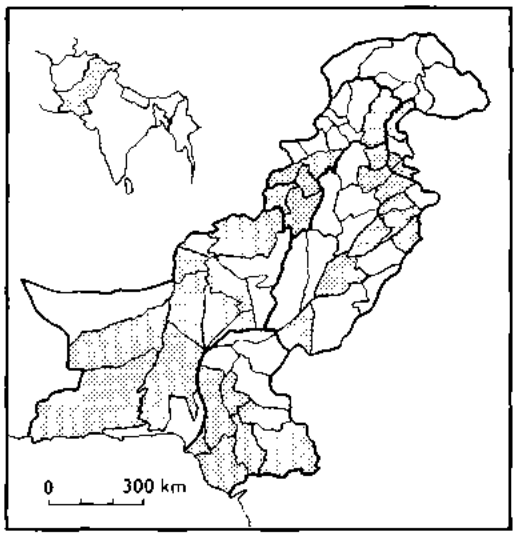


Fig. 25.10. Districts of Pakistan (shaded) visited by members of the International Commission in December 1976.

their knowledge of smallpox and of the reward offered for its detection.

Results of searches

The Commission's teams found pockmarks in 99 out of more than 7000 children under the age of 15 (1.4%). Only 5 children under 5 years of age were found to have pockmarks; all were recorded cases from outbreaks which had occurred before October 1974. No undisclosed outbreaks were discovered during the Commission's surveys. A substantial number of recent outbreaks were reinvestigated and details of the cases verified in the records. No missed cases were discovered. The checks for vaccination scars showed that a very high coverage had been achieved among adults and older children, somewhat less satisfactory levels being found in some areas among children under 5 years of age.

The evidence of variolation scars in adults confirmed that this practice had been common many years previously in parts of Baluchistan, in certain of the tribal areas of North-west Frontier Province and in a few communities in other provinces. Variolation scars were seen in children in 2 of the areas associated with documented episodes in 1974 but, despite careful searches, not in children elsewhere. Ten former variolators were interviewed. They stated that variolation material did not remain potent for more than a year at the most and that the practice had been abandoned. Signs advertising the reward for

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Plate 25.5. Vaccination scar and facial pockmark survey being conducted by members of the International Commission for the Certification of Smallpox Eradication in Pakistan, December 1976.

	Population (millions)	Year 1973	1974	1975
BANGLADESH	76.6	32 711	16 485	13 798
BHUTAN	1.2	6	3	—
BURMA	30.8	—	—	—
INDIA	618.8	88 114	188 003	1 436
NEPAL	13.0	277	1 549	95

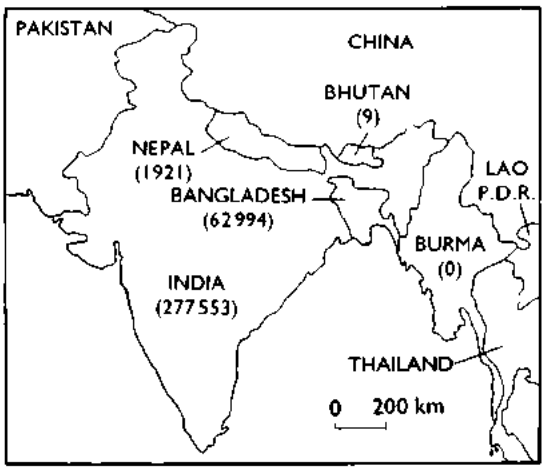


Fig. 25.11. Numbers of cases of smallpox reported from 4 countries in the Indian subcontinent and Burma, 1973–1975. Population data for 1975 from United Nations (1985).

reporting smallpox were seen in many of the places visited and, although their distribution was uneven, knowledge of the reward was widespread.

Conclusions

The Commission concluded that the smallpox eradication programme had achieved its goal in October 1974 and that there had been no smallpox transmission in Pakistan since that time. Although population movements across the long border between Pakistan and India were very limited, the Commission recommended that primary vaccination should be continued at least until the whole of Asia had been certified to be free of smallpox.

CERTIFICATION IN THE REST OF THE INDIAN SUBCONTINENT AND BURMA

Bangladesh, Bhutan, Burma, India and Nepal, contiguous countries in a vast area (Fig. 25.11) in which smallpox had been endemic for centuries, with frequent transmission across the international boundaries, were dealt with next. The last case of smallpox in India was reported in May 1975. Nepal and Bhutan experienced a number of importations from northern India as late as 1974 and 1975. In Bangladesh, freed from smallpox in 1971, major epidemics developed from 1972 onwards as a consequence of importations from West Bengal and Bihar. The last outbreaks of smallpox in Burma occurred in 1969, when an importation from Bangladesh resulted in 68 cases. Thus, in these 5 countries, continuing freedom from the disease depended very much on whether the adjacent country was smallpox-free. Because of India's large size and vast population, the smallpox situation in that country greatly influenced that in the others. Bhutan recorded its last smallpox case in February 1974, Nepal in April 1975 and India in May 1975 (Table 25.21). For certification purposes, these 3 countries were treated as a group and certified by international commissions in April 1977. Bangladesh recorded its last case in October

Table 25.21. Number of reported cases of smallpox in 4 countries of the Indian subcontinent and Burma, 1967–1976

Country	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976
Bangladesh	6 648	9 039	1 925	1 473	0	10 754	32 711	16 485	13 798	0
Bhutan	14	0	0	0	0	0	6	3	0	0
Burma	2	181	68	0	0	0	0	0	0	0
India	84 902	35 179	19 281	12 773	16 190	24 407	88 114	188 003	1 436	0
Nepal	110	249	163	76	215	399	277	1 549	95	0

Plate 25.6. Planning workshop for precertification activities in India and Nepal, held in Kathmandu, Nepal, 29 January – 2 February 1976.
Left to right, front row: N.A. Ward (WHO), R.N. Basu (India), Than Win (Burma), A.J. Hajian (WHO), E. Shafa (WHO), S.O. Foster (WHO), P.N. Shrestha (Nepal), A.K. Joarder (Bangladesh), D.A. Henderson (WHO), M.I.D. Sharma, (India), D.J.M. Tarantola (WHO), M. Sathianathan (WHO), Z. Ježek (WHO), R. Thapa (Nepal), L.B. Brilliant (WHO).

1975 and was certified in December 1977. Because of its contiguity, Burma was certified together with Bangladesh.

INDIA, NEPAL AND BHUTAN

India

The last case of smallpox in India occurred in May 1975 and the country was certified to be free of smallpox in April 1977. Precertification activities were recognized as an essential follow-up to eradication, and WHO support in terms of personnel and funds (provided by Sweden) was continued. About 60 epidemiologists (20 international and 40 national) participated in the 2-year preparation for certification, a detailed account of which is given in Basu et al. (1979). Ježek, Dr Lev Khodakevich and Dr Nicholas Ward were responsible for coordinating the activities on behalf of WHO. At the national level, Dr R. N. Basu took full responsibility for certification preparations. Detailed planning was discussed at an informal workshop held in Kathmandu, Nepal, from 29 January to 2 February 1977 (Plate 25.6).

Precertification activities

A thorough programme was undertaken, consisting of the following components: intensified surveillance for cases of fever with rash, active searches for possible cases of smallpox, laboratory testing of suspected cases of smallpox, and finally a comprehensive assessment of all this work by a national assessment commission.

Surveillance of outbreaks of fever with rash. A system for the surveillance of all cases of fever associated with a rash was introduced throughout India in January 1976. This required each health worker to report all such cases, as well as cases of and deaths from chickenpox, in addition to all cases suspected of being smallpox. Special registers for cases of fever with rash were established at each basic reporting unit—namely, 5323 primary health centres, 1005 municipal health offices, 1050

DAS PHOTO STORE

Back row: A. Nasiruddin (Bangladesh), K. Rahman (Bangladesh), M. Bari (Bangladesh), A. Moazzem (Bangladesh), M.C. Appa Rao (India), W. Hardjotanojo (WHO), A.G. Achari (India), M. Dutta (India), R.R. Arora (India), V.A. Moukhopad (WHO), C.K. Rao (India), P. Kunasol (Thailand), C. Sthapit (Nepal), M.K. Al Aghbari (WHO), B. Rana (Nepal), M.K. Singh (India), K. Dixit (Nepal), L.N. Khodakevich (WHO), Unidentified person, I.B. Khatri (Nepal), D.P. Olsen (WHO), J.S. Weisfeld (WHO), T. Chettri (Nepal), Y. Selivanov (WHO), T.S. Jones (WHO), D.A. Breach (WHO), H.D. Mehta (WHO), A.M. Monnier (WHO), A.M. Scardaci (WHO), J.S. Friedman (WHO).

selected hospitals and 797 other peripheral notification posts, as well as 428 smallpox eradication programme offices based in district and state health establishments.

Active search operations. Active search operations, initiated as part of the eradication campaign in the autumn of 1973 (see Chapter 15), continued throughout the period from May 1975, when the last case was discovered in India, until April 1977, when the International Commission visited the country. The frequency of these active search operations is shown in Fig. 25.12.

Compared with the searches in 1973 and 1974 during the eradication programme, those carried out in 1975 and 1976 were both much more extensive and more intensive, and included 3 country-wide searches conducted in the autumn of 1975, the spring of 1976 and the autumn of 1976. These involved some 110 million households in more than half a million villages and 2600 urban areas. The major national search operations aimed at recording not only suspected cases of smallpox, but also any cases of fever with rash, including chickenpox, measles and certain skin diseases. In addition, individual states intermittently carried out their own searches. Diagnoses were verified only by higher-level health officers. A reward of 1000 rupees (US$100), introduced in July 1975, was offered to both searchers and health officers and the general public, and provided a strong incentive for the searchers to discover cases of smallpox, if they did occur (Plate 25.7).

More than 95% of all the villages in India were searched during each country-wide search. No smallpox cases were found although tens of thousands of cases of chickenpox were seen. The results of the subsequent assessment of some 10% of the villages already searched indicate that about 70% of the families knew about the smallpox reward and where to report the disease should they find it. Fig. 25.13 shows the percentages of households assessed as having seen the searchers in each survey, by district. The coverage by searchers was good in the 1975 search and improved still further in those carried out in 1976 (Table 25.22).

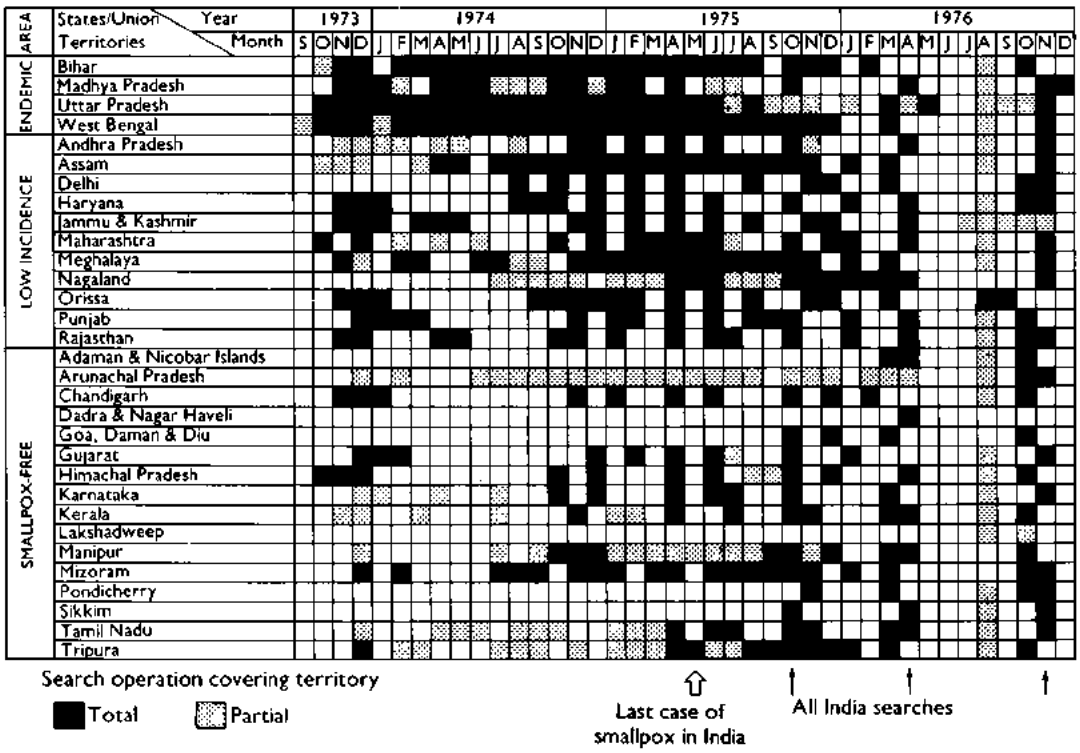


Fig. 25.12. Frequency of active search operations in India, 1973–1976. (From Basu et al., 1979.)

Table 25.22. India: country-wide searches, 1975–1976

	October–November 1975	March–April 1976	October–November 1976
Target area:			
Total number of villages	615 919	692 189	674 491
Number of villages searched	604 459	682 151	668 332
Percentage searched	98.1	98.5	99.1
Search findings:			
Number of smallpox cases	0	0	0
Number of chickenpox cases	29 682	379 297	41 485
Number of chickenpox outbreaks	15 721	118 642	20 076
Numbers of personnel employed:			
Searchers	98 103	106 142	115 347
Supervisors	21 383	28 060	29 046
Assessors	5 163	7 974	8 048
Total	124 649	142 176	152 441
Assessment:			
Number of villages assessed	71 504	81 686	107 409
Number of villages found searched	68 551	77 193	104 596
Percentage searched	95.8	94.5	97.0
Number of households questioned	1 950 613	1 867 594	3 051 753
Percentage that saw searchers	94.0	79.3	86.0
Percentage that knew of reward	73.0	80.4	83.0

During 1976, altogether 1 951 487 cases were recorded in the registers for cases of fever with rash, 60% of them following active searches, 36% following routine village visits by health staff, reports by members of the public or through the secondary surveillance system, and 4% as a result of market searches. All cases were examined by experienced health supervisors and none was found to be smallpox. The data on cases

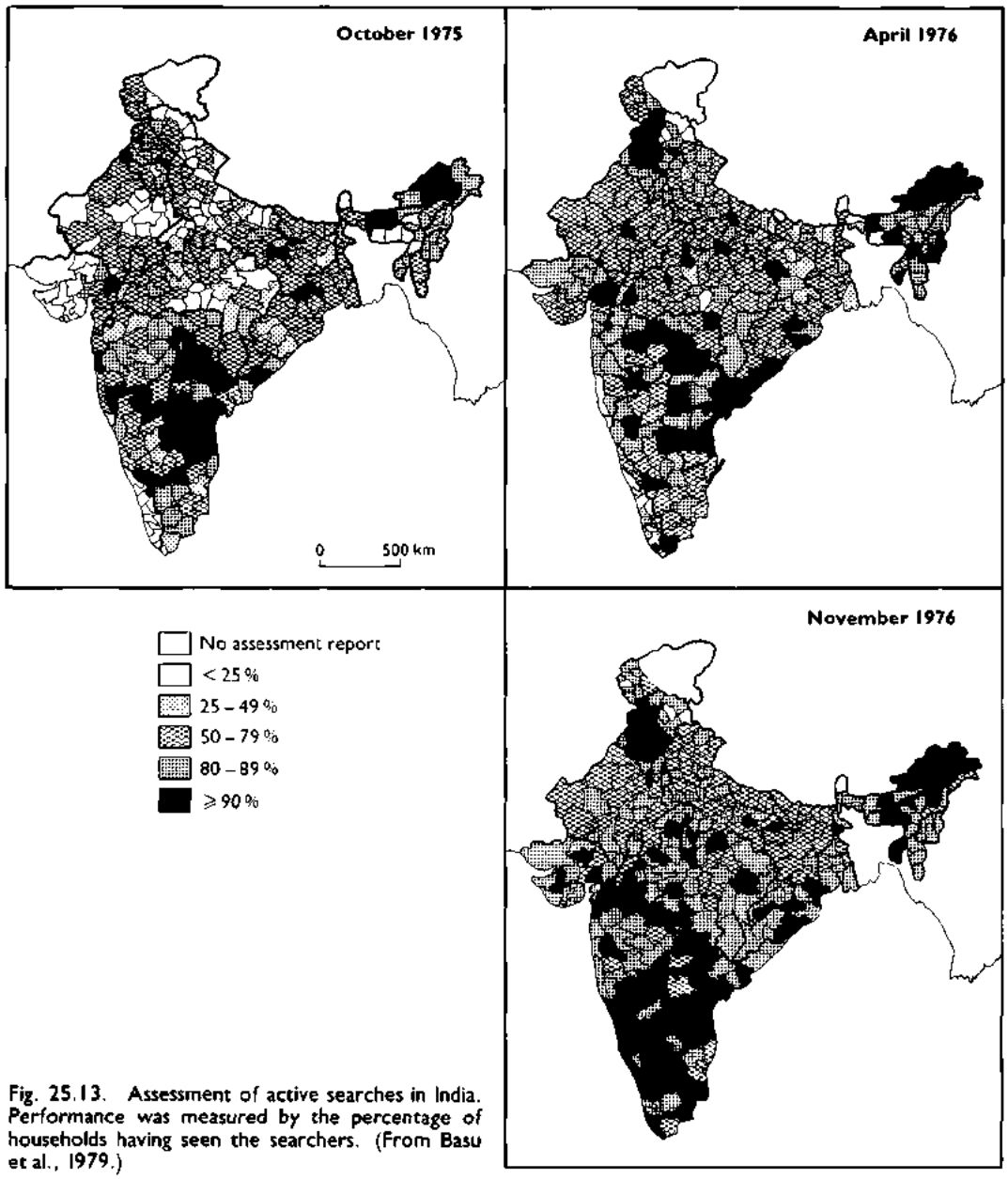
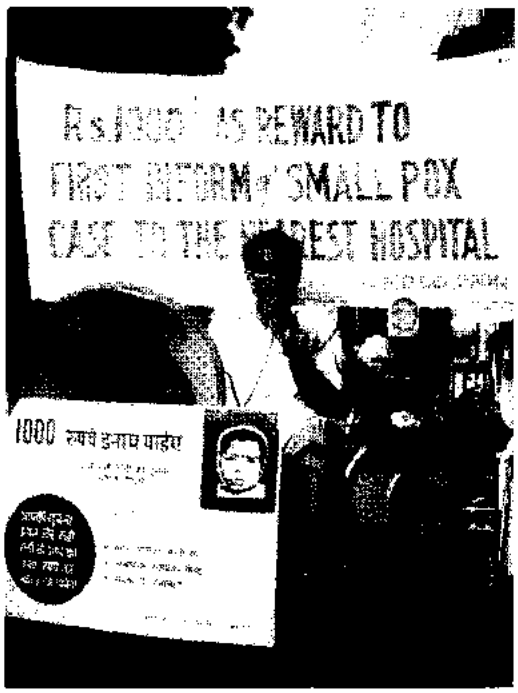


Fig. 25.13. Assessment of active searches in India. Performance was measured by the percentage of households having seen the searchers. (From Basu et al., 1979.)

entered in the registers are analysed in Table 25.23. In the same year, 519 651 localities in which these cases had occurred were visited by experienced senior health workers (37% of them by medical officers); in the first quarter of 1977, a further 322 526 localities were visited. The number and thoroughness of these investigations made it difficult to believe that smallpox could have persisted in India for 2 years without being detected.

Furthermore, 520 cases (102 suspected clinically to be smallpox and 418 deaths in chickenpox outbreaks) were investigated in 1976 by experienced epidemiologists associated with the smallpox eradication programme (Ježek et al., 1978e) and 63% of the suspected smallpox cases were found to be due to chickenpox; none was smallpox.

As would be expected from the known seasonal incidence of the disease, by far the largest number of chickenpox outbreaks and cases occurred during the spring search (March–April 1976). In April 1976, a special study was carried out in the state of Kerala,



Z. JEŽEK

Plate 25.7. During the eradication programme in India the reward had gradually been increased from 10 to 100 rupees by the end of 1974. In July 1975, after smallpox was believed to have been eradicated from India, the reward was increased to 1000 rupees.

in which chickenpox deaths appeared to be unusually frequent, especially in adults (White, 1978). The investigation revealed that deaths attributed to chickenpox had been correctly diagnosed.

Special searches. In addition to the search operations just described, special searches were carried out in certain parts of the country which, for geographical reasons, were relatively inaccessible. These had posed problems for surveillance during the eradication campaign and required special attention during the precertification activities. First, surveillance activities were reinforced in the Andaman and Nicobar Islands, Ladakh, Mizoram and Sikkim (Ježek & Kanth, 1978; Ježek et al., 1978b). Secondly, 353 sites of outbreaks at the end of 1974 and in 1975, dispersed over 55 districts located in 20 states or Union territories, were systematically reinvestigated in the latter part of 1976 (Ježek et al., 1978c). Investigations that included interviews with more than 128 000 households and the physical checking of over a quarter of a million persons yielded no evidence of hidden foci or missed outbreaks.

Laboratory diagnosis. During the Intensified Smallpox Eradication Programme, the diagnosis of smallpox had been confirmed by laboratory investigations mainly in suspected cases which had occurred *in* smallpox-free areas or areas of low incidence. The number of such investigations was substantially increased during the precertification activities, especially in the first quarter of 1977 (Table 25.24). From January 1976 onwards, special instructions were issued calling for specimens to be collected from a representative patient in every outbreak of suspected smallpox, from every chickenpox outbreak in which deaths occurred, and from every outbreak of a vesicular disease in which containment action was taken, even if by mistake. The last instruction was based on the fact that, before the active searches in 1973, vaccinators and health officials had occasionally concealed smallpox cases but carried out containment vaccination in the hope that the outbreak would subside.

In January 1975, the government of India arranged that the National Institute of Communicable Diseases should take sole responsibility for testing smallpox specimens from India; for this purpose, the Institute used both gel precipitation and virus isolation on the chorioallantoic membrane. The WHO collaborating centres in Atlanta and Moscow also tested many specimens and carried out electron microscopic examinations in addi-

Table 25.23. India: entries in registers of cases of fever with rash during 1976 and the first quarter of 1977[a]

Period	Total number of cases	Chickenpox		Measles		Other skin diseases		Miscellaneous cases[b]
		Cases	Deaths	Cases	Deaths	Cases	Deaths	
1976	1 951 487	862 155	433	519 597	3 122	146 855	175	422 880
1977 (to end of March)	1 189 072	638 060	105	481 743	619	31 417	..[c]	37 852

[a] Based on Ježek et al. (1978g).
[b] Malaria, diarrhoeal diseases, false alarms.
[c] .. = data not recorded.

Table 25.24. India: results of laboratory tests for variola virus, January 1975–April 1977

Year	Number of cases in which virus or specific antibodies were detected[a]				
	Total	Variola virus	Vaccinia virus	Varicella–zoster virus	Herpes simplex virus
1975	702	141	2	45	1
1976	640	0	4	106	4
1977 (end end of April)	1 385	0	..	..	..

[a] .. = data not recorded

tion to the other two methods. In principle, duplicate specimens were collected from each suspected case, one being tested by the National Institute of Communicable Diseases and the other by one of the WHO collaborating centres. For virus isolation, the results obtained were in full agreement. Laboratory investigations of 2025 specimens provided no evidence of smallpox in India during 1976 and 1977.

Variolation and laboratory stocks. In contrast to the situation in Afghanistan and Pakistan, variolation had not been a problem in India during the past few decades and no special inquiries were required. However, the situation with regard to laboratory stocks of variola virus was carefully evaluated and steps were taken in 1976 to ensure that all such material was destroyed.

The national commission

Before the International Commission's visit to India, scheduled for April 1977, the Indian government organized a national commission for the assessment of the smallpox eradication programme in India (Basu & Khodakevich, 1978a). This consisted of 32 members from the Union government of India and 12 state governments and from WHO (Plate 25.8). Both Dr Jan Kostrzewski (who was to be chairman of the International Commission shortly to be set up) and Arita also attended a coordination meeting of the national commission in January 1977, since successful certification of smallpox eradication in India by the International Commission was clearly an important milestone in certification in the world as a whole and thorough preparation was essential. The national assessment took place over the period from 13 December 1976 to 8 January 1977.

After a preliminary assessment of the situation, teams from the national commission investigated selected districts to assess their surveillance activities (Fig. 25.14). Although their observations might not be seen as completely impartial by observers outside India, the members of the national commission teams were extremely critical in assessing what had been accomplished since, if they failed to discover any deficiencies, they would be held responsible.

The national commission found no evidence of continuing smallpox transmission and India was considered ready to receive the International Commission in April 1977.

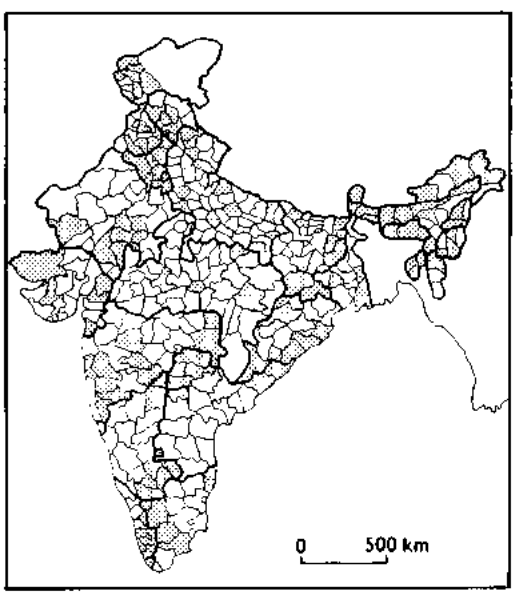


Fig. 25.14. Districts of India (shaded) visited by the National Commission for the Assessment of the Smallpox Eradication Programme, 13 December 1976 – 8 January 1977.

WHO

Plate 25.8. WHO personnel participating in the meeting on 20–21 January 1977 of the National Commission for the Assessment of the Smallpox Eradication Programme in India. *Left to right:* N.A. Ward, Z. Ježek, L.N. Khodakevich, J.S. Friedman.

Nepal

After what was regarded as the last case of smallpox in Nepal had been recorded in April 1975, surveillance was continued until the International Commission visited the country in April 1977. During the eradication programme, the country had been divided into 3 areas (see Chapter 15): (1) densely populated areas of low altitude adjacent to the Indian states of Uttar Pradesh and Bihar—i.e., the areas most vulnerable to smallpox importations; (2) high Himalayan mountainous areas with sparse populations and the least likely to experience importations; and (3) areas intermediate between (1) and (2). This subdivision was retained throughout the precertification surveillance period.

A similar surveillance strategy was adopted in all areas, active searches being carried out by means of house-to-house visits. The 3 main groups of surveillance workers were: smallpox eradication programme staff, malaria control staff, and health workers assigned to integrated health activities. Dr P. N. Shrestha, director of the national smallpox eradication programme, ensured that the best use was made of available health workers in order to strengthen the surveillance activities. Mr Jay Friedman, a WHO technical officer who had been located in Nepal since 1972, remained there until the International Commission visited the country, and contributed to the success of the undertaking. No evidence of smallpox transmission was found at any time during the precertification activities.

In 1975 a special pockmark survey was conducted among 2350 Tibetan refugees; this found no evidence of smallpox transmission in Tibet (Xizang Autonomous Region) more recently than 1961 (see Chapter 27). This was extremely important, since little was known of the incidence of smallpox in China at that time. The survey indicated that the chance of smallpox importation from Tibet was extremely small.

Bhutan

The last known case of smallpox in Bhutan occurred in February 1974, when 3 cases were introduced from Assam, India. In 1976 the

governments of Bhutan and India began discussions on the development of a special surveillance programme in preparation for certification. In August 1976 an Indian team, headed by Dr Basu, visited Bhutan to finalize the surveillance plan. An active search by means of house-to-house visits was carried out between September and December 1976, concentrated on the southern part of the country, where people moved freely across the border with India. A total of 23 surveillance workers visited about 800 villages; out of 45 000 persons seen, 11 were pockmarked. However, there was no indication of smallpox transmission after the last case in 1974.

Visit of the International Commission

An International Commission consisting of 16 members from 16 countries visited Bhutan, India and Nepal in March–April 1977; groups of Commission members visited Bhutan from 28 to 30 March, Nepal from 6 to 13 April and India from 6 to 20 April. For political reasons, Bhutan and India were certified separately. Since at that time only persons of Indian nationality were allowed to visit Bhutan, Lieutenant General R. S. Hoon, an epidemiologist serving in the Indian Defence Forces and a member of the International Commission, visited Bhutan together with Dr Basu, after which he participated in the investigation of the adjacent Indian state of Arunachal Pradesh.

All 16 members of the International Commission met first in New Delhi to assess the situation and plan field visits. During the field visits, each member was accompanied by national and WHO personnel who had either been members of the Indian national commission or were WHO epidemiologists who had worked in India during the precertification activities. In order to achieve maximum coverage, each member visited different areas in one or two states or union territories over a period of some 2 weeks (Fig. 25.15) before all the members of the Commission reassembled in New Delhi. Dr Kostrzewski with 2 members of the Commission and Ježek, who had been engaged in certification activities in India, visited Nepal, and then resumed their Indian field investigations. During the field visits, the Commission members concentrated on assessing the extent

WHO

Plate 25.9. Members of the International Commission for the Certification of Smallpox Eradication in India and Bhutan, and Nepal, 23 April 1977, with the Director of the WHO Regional Office for South-East Asia. *Left to right, front row:* H. Flamm (Austria), J. Červenka (Czechoslovakia), W.A.B. de Silva (Sri Lanka), R.S. Hoon (India), F. Fenner (Australia), J. Kostrzewski (Poland), V.T.H. Gunaratne (WHO Regional Director), D.M. Mackay (United Kingdom), A.M. Mustaqul Huq (Bangladesh), R. Roashan (Afghanistan), V.M. Zhdanov (USSR), U Thein Nyunt (Burma); *back row:* W. Koinange (Kenya), H.B. Lundbeck (Sweden), T. Kitamura (Japan), D.J. Sencer (USA), M.F. Polak (Netherlands).

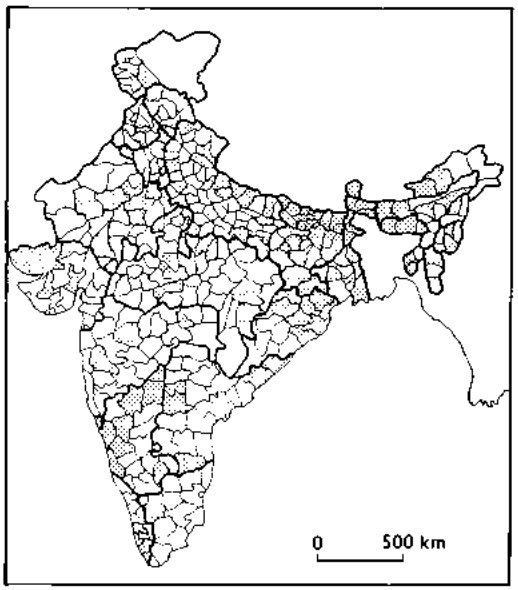


Fig. 25.15. Districts of India (shaded) visited by members of the International Commission, 4–23 April 1977.

and quality of the search and surveillance activities by examining records and interrogating several categories of staff at state, district, municipal, primary health centre and subcentre levels. They independently assessed the validity of statements about community awareness of smallpox by visiting villages, schools, urban areas, bazaars, places of pilgrimage and international ports. Brief reports were produced by the various Commission members or teams and these were discussed by the Commission at a plenary session from 21 to 22 April 1977.

In Nepal, 2 teams were formed, one covering the east and the other the west, special attention being paid to areas bordering on India. The members of the Commission were unable to visit the Tibetan border, but information collected from nearby mountainous areas indicated that Tibet was smallpox-free.

On 13 April 1977 Nepal was certified by the International Commission to be free of smallpox; this was followed, on 23 April, by the certification of Bhutan and India.

Plate 25.10. J. Kostrzewski, Chairman of the International Commission, presents the Commission's report to the Minister of Health and Family Welfare of India, Shri Raj Naraian, on the occasion of the certification of eradication in that country on 23 April 1977. Shri Rajeshwar Prand, Secretary of the Ministry, is in the centre.

BURMA AND BANGLADESH

Burma

Indigenous transmission in Burma had been interrupted in 1966 by a systematic mass vaccination campaign that began in 1954 and was intensified in 1963, using locally produced vaccine of acceptable potency and heat stability. Smallpox was then reintroduced from the Chittagong Hill Tracts in Bangladesh (then East Pakistan) into the neighbouring Burmese state of Arakan, in which it caused an outbreak with 181 reported cases in 1968 and 68 in 1969. This was controlled by intensive vaccination. In 1970 a WHO team had declared Burma to be free of endemic smallpox, and no further cases had been reported since then.

Between 1968 and 1975, 51 suspected cases of smallpox were investigated by field staff and specimens examined for variola virus in the laboratory, with negative results. In 1976–1977 the government of Burma established 4 national assessment teams, which visited every state and division in Burma, carried out pockmark surveys among children in the age group 5–14 years, and assessed the vaccination coverage and evidence relating to cases of suspected smallpox. The reports of these national assessment teams provided the basis for the investigations by the International Commission. In order to coincide with certification in Bangladesh, the Commission's visit was arranged for November 1977.

Bangladesh

The last case of smallpox in the Asian continent occurred in Bangladesh in October 1975; it was also the last case of endemic variola major in the world. As in India, the smallpox eradication programme retained its personnel and organization for the next 2 years in order to continue surveillance and determine whether the supposed last case really was the last one. Precertification activities in Bangladesh have been described by Joarder et al. (1980). Between October 1975 and May 1976, a large number of international and national staff were engaged in the search operations (Table 25.25). Among the many dedicated persons who contributed to the certification activities in Bangladesh, special mention may be made of Dr A. M. Mustaqul Huq, who had promoted the eradication programme since 1967, initially as programme manager and later as Director of Health Services (Preventive), and Dr Daniel Tarantola, a WHO epidemiologist, who stayed in Bangladesh until certification had been completed.

Active searches

Between October 1975 and October 1977 active country-wide searches for unreported cases, based on house-to-house visits, were organized on 8 occasions (Fig. 25.16). In each search, 50 000–60 000 health workers were mobilized. In the searches in December 1976–January 1977 and May–June 1977, deaths from chickenpox or measles were also investigated by interviewing a family member and/or taking specimens from other cases in the outbreak. A total of 56 deaths from chickenpox and 480 deaths from measles were investigated, as well as 63 deaths known only to have been caused by a disease in which there was fever with rash (Table 25.26). None of the fatal cases was due to smallpox.

After the search had been completed, the assessment team visited villages selected at random. They found that coverage by the search team varied between 78% and 87% (Table 25.26). More than 80% of the people interviewed knew about the smallpox reward.

Special searches were organized in the Chittagong Hill Tracts. The area was differ-

Table 25.25. Bangladesh: numbers of international and national epidemiologists engaged in surveillance, 1975–1977

Period	Number of WHO staff in Dhaka	Number of international field epidemiologists	Number of national epidemiologists	Total
July 1975	10	65	15	90
January 1976	7	21	20	48
July 1976	3	9	24	36
January 1977	3	7	32	42
July 1977	3	9	31	43

ent from other parts of Bangladesh in that the population was sparse, communications were poor and the health infrastructure was rudimentary. No evidence of smallpox was found.

Surveillance in Dhaka and urban areas

The active searches just described were carried out mainly in rural areas. However, it was in the major urban areas, including Dhaka in which housing was extremely congested and into and out of which tens of thousands of rural inhabitants flowed daily, that smallpox transmission had been maintained in the past, unknown to the central health services (see Chapter 16). In Bangladesh, moreover, the municipal health services were administratively independent of the district or regional health authorities, those responsible for smallpox eradication being no exception.

Surveillance in the municipalities therefore became an extremely important pre-certification operation. The methods employed were daily visits to infectious diseases hospitals and cemeteries to check on the causes of recent admissions, deaths and burials, and the use of surveillance teams, of which there were 2 in Dhaka and 1 in each of the other 5 major municipalities. They made regular visits to high-priority areas, including the bustees (the shanty towns, whose inhabitants were usually unfamiliar with the urban health facilities and, of course, with the reporting of information on rashes), areas of low literacy in which written publicity probably failed to reach the people, and places where the population congregated daily or intermittently in large numbers. House-to-house searches were conducted periodically in all municipalities, usually immediately after the national house-to-house searches in rural areas.

This schedule allowed surveillance teams and epidemiologists to devote additional time to the supervision and assessment of urban searches. None of these search activities disclosed evidence of continuing smallpox transmission after the case in October 1975.

Pockmark survey

A facial pockmark survey of 465 892 persons aged 0–19 years, based on 1550 sampling sites all over Bangladesh, was conducted in July–December 1976. None of the 939 persons with facial pockmarks who had

Table 25.26. Bangladesh: house-to-house searches, May 1975–October 1977

Date	Search schedule		Results of investigation[a]					Assessment (random)			Percentage of households aware of:	
	Number of villages	Number of outbreaks	Total number of cases of fever with rash	Smallpox	Chickenpox	Measles	Other types of rash	Number of villages assessed	Number of houses assessed	Percentage of houses visited during search	reward	where to report
October 1975	62 690	10 909	10 652	0	2 376	.. [b]	8 276	1 749	34 362	78	79	72
Nov.–Dec. 1975	61 453	16 039	16 428	0	4 688	.. [b]	11 760	1 688	32 867	84	81	80
January 1976	62 204	31 372	33 283	0	19 007	9 543	4 733	1 515	32 111	85	87	79
March 1976	60 619	16 998	58 130	0	43 204	13 714	2 212	1 455	28 737	84	87	78
May–June 1976	60 562	11 337	28 929	0	17 038	9 436	2 505	1 378	27 301	87	90	80
Dec. 1976–Jan. 1977	61 604	8 131	20 312	0	11 835 (15)	6 654 (245)	1 823 (24)	1 466	29 095	83	86	76
May–June 1977	57 041	9 564	23 212	0	11 839 (41)	8 557 (235)	2 816 (39)	1 481	28 161	85	90	81
October 1977	57 780	?	3 266	0	1 334 (4)	1 069 (23)	863	1 442	28 763	82	88	81

[a] Numbers of deaths shown in parentheses.
[b] .. = data not recorded.

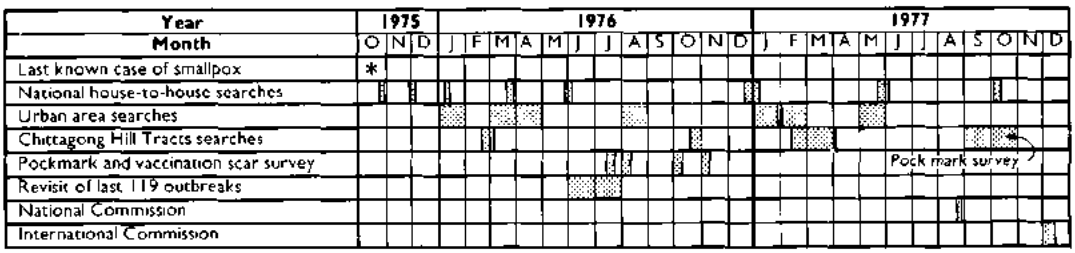

Year
1975
1976
1977
Month
O N D J F M A M J J A S O N D J F M A M J J A S O N D
Last known case of smallpox
National house-to-house searches
Urban area searches
Chittagong Hill Tracts searches
Pockmark and vaccination scar survey
Revisit of last 119 outbreaks
National Commission
International Commission
Pock mark survey

Fig. 25.16. Precertification and certification activities in Bangladesh between October 1975 and December 1977. August 1977: active searches, visits by members of the National Commission; December 1977: visits by members of the International Commission. (From Joarder et al., 1980.)

contracted smallpox after 1971 had been infected after 1975 (Table 25.27).

Laboratory diagnosis

Between January 1976 and November 1977, 2462 specimens were investigated by the smallpox diagnostic laboratory in the Institute of Public Health, Dhaka, and 698 were tested by WHO collaborating centres in Atlanta and Moscow (Table 25.28). In none was variola virus found, although vaccinia virus was recovered from vaccination scabs and herpesvirus particles were seen in many of the specimens examined by electron microscopy in the WHO collaborating centres.

Table 25.27. Bangladesh: results of pockmark survey, 1976[a]

Date of attack	Number of persons with pockmarks
Before 1972	3 367
1972	417
1973	329
1974	139
1975	54
1976	0

[a] Target population: 0–19 years; sample: 1% random cluster sample; number examined: 465 892.

The national commission

A national commission of 52 members met in August 1977 to assess the smallpox eradication programme in Bangladesh. Teams from the national commission visited all districts, 54 subdivisions, 81 *thanas* and each of the 4 major municipalities in Bangladesh. After meeting again in Dhaka, the national commission expressed its satisfaction with the evidence that had been assembled to support the contention that there had been no smallpox transmission in Bangladesh after October 1975.

Visit of the International Commission

After a briefing session at the WHO Regional Office for South-East Asia, in New Delhi, a 9-member International Commission visited Burma from 21 to 30 November 1977 and Bangladesh from 1 to 14 December 1977. One representative from Burma and one from Bangladesh were included in the Commission because two politically disturbed areas—Chin State in Burma and the Chittagong Hill Tracts in Bangladesh, with a common border—could be visited only by nationals of the country concerned. In addition, the representative of each country was expected

Table 25.28. Bangladesh: results of tests of specimens from suspected cases of smallpox by the Institute of Public Health, Dhaka, and WHO collaborating centres, 1976–1977

Year	Institute of Public Health, Dhaka			WHO collaborating centres			
	Number examined	Number positive for variola virus	Number positive for vaccinia virus	Number examined	Number positive for variola virus	Number positive for vaccinia virus	Number with herpesvirus particles
1976	406	0	16	163	0	7	32
1977	2 056	0	9	535	0	1	211

WHO

Plate 25.11. Participants in the National Commission for Smallpox Eradication, Bangladesh, 21–27 August 1977. *Left to right, front row:* H.D. Mehta (WHO), A.U.M. Khairul Bashar, Sarafat Ali, A.S.M.A. Hakim, A.E. Suliman (WHO), M. Khabiruddin, A.J.M. Mizanur Rahman, A.K.M. Kefayetullah, M. Abul Hossain, Nayeb Ali, V. Zikmund (WHO); *middle row:* S.M. Nuruzzaman, Nayeb Ali, D.J.M. Tarantola (WHO), M. Sathianathan (WHO), A.M. Mustaqul Huq, M. Zakir Husain, A.K. Joarder, K.M. Rahman, A.A. Miah, Serajul Haque; *back row:* Sarder Alauddin, Mozammel Huq, S.N. Ray (WHO), A.K.M. Lutfar Rahman Talukder, C.-T. Chong (WHO), A.I. Gromyko (WHO), M. Moizuddin, A.M.H. Nurul Alam, N.M.P. Mendis (WHO), Golam Nabi, G.R.A. Taylor (WHO), M. Shahidullah, Subrata Chakma, A.A. Stroganov (WHO), Mustafizur Rahman, Anwarul Islam, A.I.M.M. Islam, M.Q. Elahi, M.A. Latif Mia, Mobarak Ali, M. Asaduzzaman, Aung Myat (WHO), A.B.M. Mofizur Rahman, A. Mannan, M.A. Fattah Khan, A.J.R. Wylie (WHO), M. Serajul Islam, M. Aftabuddin Khan, Mofazzal Hussain, R.N. Basu (WHO).

to be particularly vigilant about the evidence of eradication in the other country.

Burma

Field trips by Commission members covered an area with a population of more than 4 million in addition to the city of Rangoon (population 3.2 million). Together, International Commission members and national teams covered all the states and divisions of Burma. One of the main activities of the Commission members during their field visits was a pockmark survey, in which more than 58 000 persons were seen (5000 preschool children, 29 000 schoolchildren and 24 000 adults), among whom 399 pockmarked persons were identified. The majority of these (96.5%) had suffered from smallpox before 1963, the most recently infected being a person who had contracted the disease during the outbreak in Arakan in 1968. Extensive questioning found no evidence of the occurrence of smallpox in Burma after 1969.

Earlier in 1977 national assessment teams had examined 1.97 million children aged 5–14 years without finding any with facial pockmarks. That the International Commission found 399 and the national commission none is explained in part by the fact that only 14 of those with facial pockmarks were under 14 years of age. It is also possible, however, that the definition of pockmarks was misunderstood during the national survey so that it did not give a truly representative picture of the prevalence of pockmarked persons.

Apart from this inconsistent result, the Commission was satisfied with the surveillance activities carried out by the Burmese health staff and found no evidence of smallpox transmission after 1970. Burma was certified to be free of smallpox.

Bangladesh

After completing its work in Burma, the Commission met in Dhaka for 2 days at the beginning of December for briefing, then divided into 9 teams, each consisting of a Commission member, a WHO smallpox eradication programme officer, a national

epidemiologist and the local officers concerned. These teams travelled extensively throughout Bangladesh (Fig. 25.17) and made thorough investigations, particularly in vulnerable areas in which transmission of smallpox might be continuing. Extensive questioning revealed that the people's knowledge of the reward and of where to report suspected cases was very good. Pockmark surveys of some 50 000 persons under 20 years of age, of whom 2000 were less than 2 years old, found 575 pockmarked persons, none of whom had contracted smallpox later than 1975.

Scrutiny of documentation and supporting records showed that, with few exceptions, a high level of surveillance had been maintained by the national authorities throughout the period since the last known case.

The results of the field visits by the Commission were consistent with the national records, and on 14 December 1977 Bangladesh was certified to be free of smallpox. This action formally set the seal upon the end of endemic variola major in the world.

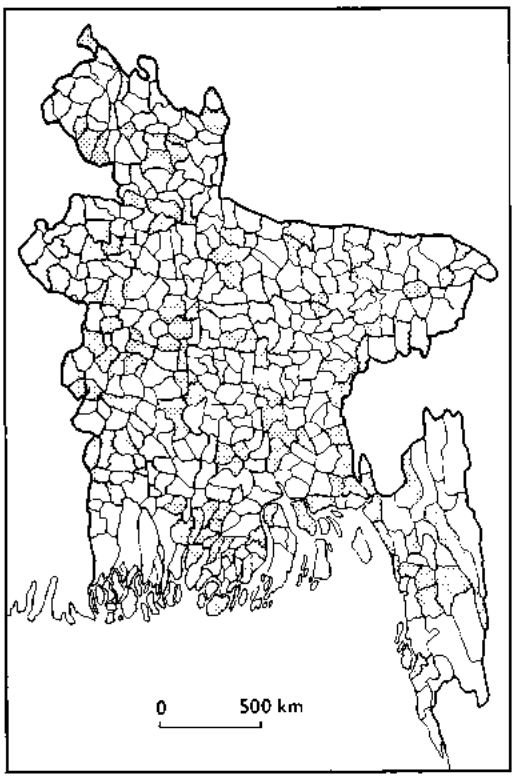


Fig. 25.17. *Thanas* in Bangladesh (shaded) visited by members of the International Commission, 1–14 December 1977. (From Joarder et al., 1980.)

CONCLUSIONS

These certification activities, which dealt with several of the former major endemic countries in the world, provided detailed information about the elimination of smallpox in the countries concerned and the methodologies for obtaining the data required by international commissions so that they could properly evaluate the likelihood that smallpox had been eliminated, both from countries in which it had recently been endemic and from those in which the last outbreak had occurred several years earlier. At the time the Consultation on the Worldwide Certification of Smallpox Eradication was held, in October 1977, preparations were well advanced for international commissions to visit other regions of Africa and Asia. It was on the basis of the knowledge and experience of certification gained between 1973 and 1977 that the Consultation was able to plan a logical series of operations that would ultimately provide the World Health Assembly with the information that would allow it to declare that smallpox had been eradicated from the world.

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CHAPTER 26

CERTIFICATION OF 29 COUNTRIES IN AFRICA AND ASIA: 1978–1979

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INTRODUCTION

By June 1977 international commissions had already visited or were preparing to visit all the previously endemic countries and countries at special risk. However, as has been explained in Chapter 24, there was a need to determine what measures should be taken in order to certify that the transmission of smallpox had been interrupted for at least 2 years in other countries, in several of which the staff of the WHO Smallpox Eradication Programme needed outside advice on how best to deal with the situation. In addition, advice on whether global eradication could be certified needed to be, and to be seen to be, independent of the special interests of WHO personnel who were intimately involved in the global eradication programme.

These problems could be solved by establishing a global commission of respected scientists which, as one of its functions, would

advise the staff of the WHO Smallpox Eradication unit as to what data should be collected, for clearly this was a matter of judgement. Eventually, when these experts were fully satisfied that global eradication had been achieved, this conclusion would have been reached, not by WHO itself, or on the basis of the reports of a series of international commissions each dealing with one or a few countries, but by an international group of senior scientists and administrators capable of taking a global view of the problem. For this reason, the Consultation on the Worldwide Certification of Smallpox Eradication was set up in October 1977 and subsequently converted into the Global Commission for the Certification of Smallpox Eradication. This chapter and the next deal with activities undertaken at the suggestion of the Consultation and the Global Commission throughout 1978 and 1979; it was hoped that these would provide data on which the Global Commission could ultimately base its opinion that the transmission of smallpox had been interrupted everywhere in the world.

In this chapter, various operations carried out in 29 countries situated in widely separated parts of Africa and Asia (Fig. 26.1) are described. Not all were certified by formal international commissions such as those referred to in Chapter 25; other procedures—a visit by a WHO-designated expert or consultant and subsequent report, or the provision of a detailed country report—had to be used for some countries (Fig. 26.2).

Fig. 26.1. The 29 countries of Asia and Africa (including Lesotho and Swaziland) in which certification was carried out in 1978 or 1979 by international commissions, by visits by a WHO-designated expert or by the provision of a detailed country report (see Fig. 26.2).

In Africa, by mid-1977, formal certification had been successfully completed in 24 countries in western and central Africa (Chapter 25). At that time, smallpox was still occurring in Somalia, so that certification of the Horn of Africa lay in the future (Chapter 27). There remained 14 countries requiring certification, extending from the Sudan in the north to South Africa in the south, and from Angola in the west to Madagascar in the east. The strategy of certification by international commissions, as recommended by the 1977 Consultation, was followed for 10 of them (Fig. 26.2, No. 1–10), but for political and logistic reasons it was not possible to follow the Consultation's recommendations for South Africa, Namibia or Southern Rhodesia (Fig. 26.2, No. 13–15). Instead, certification by the Global Commission was based on reports prepared by Global Commission members and WHO consultants after visits arranged by the Smallpox Eradication unit. As recommended by the Consultation, eradication in Madagascar was certified by the Global Commission after receipt of a detailed country report, followed up by a visit by a WHO staff member.

For 11 countries in south-western Asia, certification by various procedures was recommended. Democratic Yemen, Yemen, Iraq and the Syrian Arab Republic (Fig. 26.2, No. 11, 12, 18 and 19) were visited by international commissions. Iran was visited by experts and certified by the Global Commission on the basis of their reports. The 6 Arab countries of the Gulf area (Fig. 26.2, No. 20–25) were required to submit a country report. At their request a more searching inquiry was made; each country carried out an intensive surveillance programme designed and supervised by a WHO epidemiologist.

For 5 countries in eastern Asia, the Consultation had recommended special certification activities. China, because of its vast size and population and its lack of contact with WHO for many years, required the special measures described in Chapter 27. There remained Thailand and the war-torn countries of Democratic Kampuchea, the Lao People's Democratic Republic and Viet Nam. The fact that there had never been a WHO-sponsored smallpox eradication programme in the 3 last-mentioned countries, and that their health systems had been compromised by prolonged

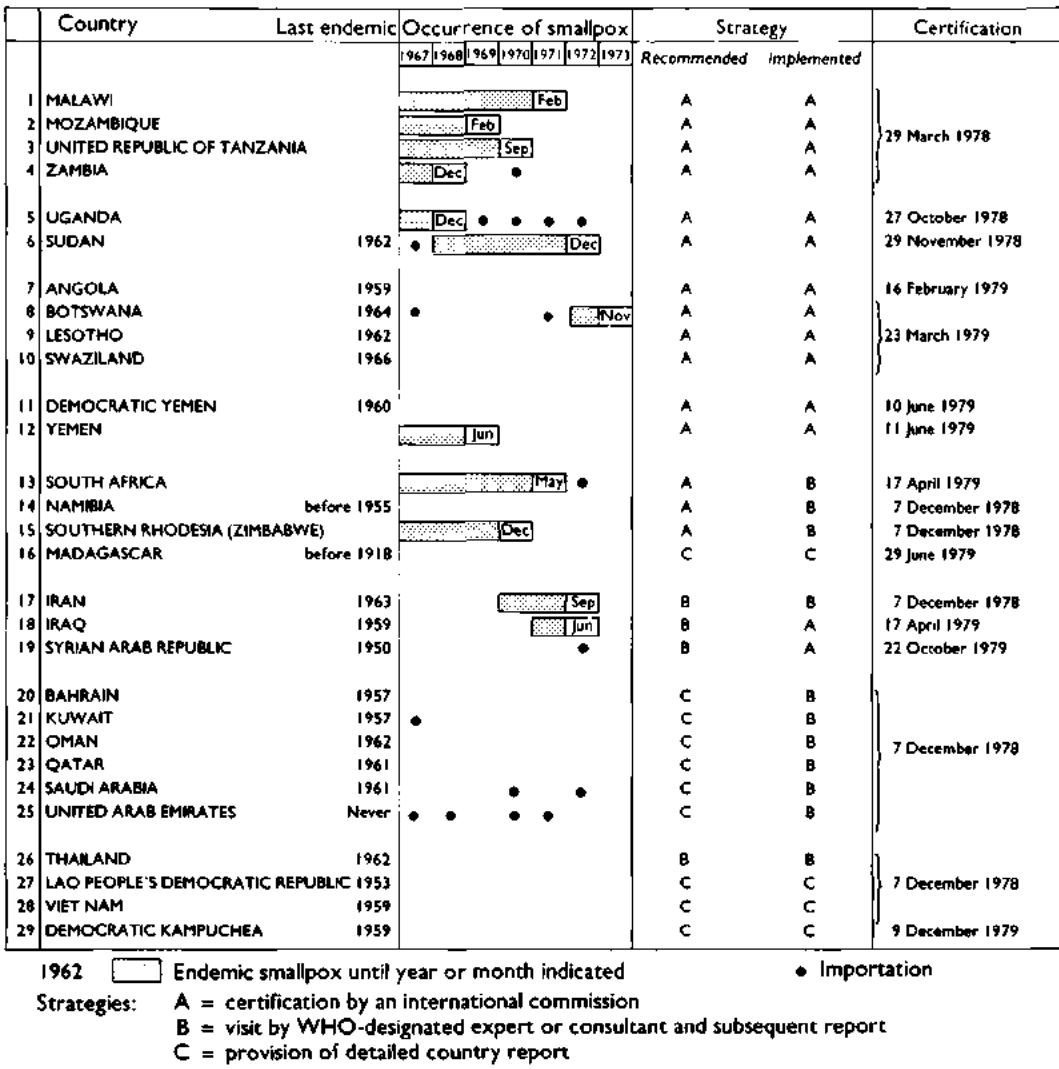

Country
Last endemic
Occurrence of smallpox
1967 1968 1969 1970 1971 1972 1973
Strategy
Recommended
Implemented
Certification
1 MALAWI Feb A A
2 MOZAMBIQUE Feb A A 29 March 1978
3 UNITED REPUBLIC OF TANZANIA Sep A A 29 March 1978
4 ZAMBIA Dec A A 29 March 1978
5 UGANDA Dec A A 27 October 1978
6 SUDAN 1962 Dec A A 29 November 1978
7 ANGOLA 1959 A A 16 February 1979
8 BOTSWANA 1964 Nov A A 23 March 1979
9 LESOTHO 1962 A A 23 March 1979
10 SWAZILAND 1966 A A 23 March 1979
11 DEMOCRATIC YEMEN 1960 A A 10 June 1979
12 YEMEN Jun A A 11 June 1979
13 SOUTH AFRICA May A B 17 April 1979
14 NAMIBIA before 1955 A B 7 December 1978
15 SOUTHERN RHODESIA (ZIMBABWE) Dec A B 7 December 1978
16 MADAGASCAR before 1918 C C 29 June 1979
17 IRAN 1963 Sep B B 7 December 1978
18 IRAQ 1959 Jun B A 17 April 1979
19 SYRIAN ARAB REPUBLIC 1950 B A 22 October 1979
20 BAHRAIN 1957 C B 7 December 1978
21 KUWAIT 1957 C B 7 December 1978
22 OMAN 1962 C B 7 December 1978
23 QATAR 1961 C B 7 December 1978
24 SAUDI ARABIA 1961 C B 7 December 1978
25 UNITED ARAB EMIRATES Never C B 7 December 1978
26 THAILAND 1962 B B 7 December 1978
27 LAO PEOPLE'S DEMOCRATIC REPUBLIC 1953 C C 7 December 1978
28 VIET NAM 1959 C C 7 December 1978
29 DEMOCRATIC KAMPUCHEA 1959 C C 9 December 1979
1962 Endemic smallpox until year or month indicated
• Importation
Strategies: A = certification by an international commission
B = visit by WHO-designated expert or consultant and subsequent report
C = provision of detailed country report

Fig. 26.2. Year of the last case of endemic smallpox and of importations of smallpox, and dates of certification of 14 countries in Africa and 15 countries in Asia according to the strategies recommended by the Consultation on the Worldwide Certification of Smallpox Eradication, October 1977, and as implemented.

warfare, made it difficult to collect data or arrange visits by WHO consultants or staff members. Thailand was visited by a member of the Global Commission; for the other countries reliance had to be placed on reports compiled from a variety of sources.

In this chapter, the certification of 14 countries in Africa is first described, then that of the 11 countries in south-western Asia and finally that of Thailand, Democratic Kampuchea, the Lao People's Democratic Republic and Viet Nam. All these operations were undertaken while, at the same time, the most intensive search activities of the whole eradication programme were being carried out in the Horn of Africa. The operations mounted to certify eradication in Ethiopia, Somalia, Djibouti and Kenya, and in China, are described in Chapter 27.

SOUTHERN AFRICA

The progress of certification in the 12 countries of southern Africa (Angola, Botswana, Lesotho, Madagascar, Malawi, Mozambique, Namibia, South Africa, Southern Rhodesia, Swaziland, the United Republic of

Tanzania, and Zambia) is shown in Fig. 26.3. No smallpox had been reported in any of these countries since 1972, except for an outbreak of variola minor in Botswana in 1971–1973, following an importation from South Africa late in 1971 (Table 26.1).

Civil unrest and, indeed, open warfare had been occurring in Angola, Mozambique and Southern Rhodesia since the mid-1970s. South Africa, Namibia (which was controlled by South Africa) and Southern Rhodesia (then regarded by the United Nations as a British colony) were not represented at the World Health Assembly. This complicated the organization of certification by international commissions. Eventually such commissions were able to visit Angola and Mozambique, where they met with no difficulties. However, there were political difficulties in organizing WHO-sponsored international commissions to certify smallpox eradication in Southern Rhodesia and Namibia, and attempts to arrange for an international commission to visit South Africa (which provided the only route of entry to Namibia) were thought unlikely to be successful or at best unduly time-consuming, owing to political factors. The recommendation of the Consultation on the Worldwide Certification of Smallpox Eradication that an international commission should visit these 3 countries (see Chapter 24) was therefore not followed. Instead, arrangements were made to obtain country reports and other necessary data by organizing visits by a Global Commission member and WHO consultants who were acceptable to the respective national governments. This proved to be quite straightforward in Southern Rhodesia and Namibia, but several visits to South Africa were needed before the requisite data could be obtained.

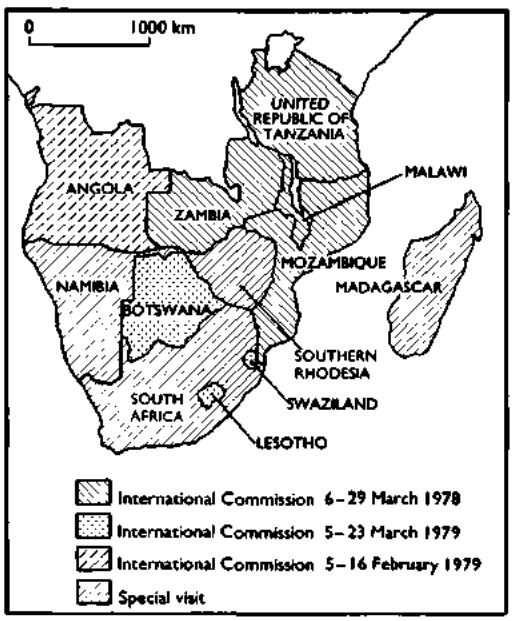


Fig. 26.3. Countries of southern Africa certified free of smallpox by international commissions or visited by a member of the Global Commission or WHO-designated expert before certification by that Commission.

Logistics

Experience in western and central Africa had shown clearly the difficulties faced by the small staff of the Smallpox Eradication unit and the relevant personnel in the WHO Regional Office for Africa in arranging simultaneous precertification activities in many countries. Furthermore, it was impossible to find experts of sufficient experience to

Table 26.1. Numbers of reported cases of smallpox in 12 countries of southern Africa, 1967–1974

Country	1967	1968	1969	1970	1971	1972	1973	1974
Malawi	38	61	65	39	10	0	0	0
Mozambique	104	145	11	0	0	0	0	0
United Republic of Tanzania	1 629	455	117	32	0	0	0	0
Zambia	47	33	0	2	0	0	0	0
Botswana	1	0	0	0	36	1 059	27	0
Lesotho	1	0	0	0	0	0	0	0
Swaziland	0	0	0	0	0	0	0	0
Angola	0	0	0	0	0	0	0	0
Namibia	0	0	0	0	0	0	0	0
South Africa	43	81	246	121	10	1	0	0
Southern Rhodesia	30	10	33	6	0	0	0	0
Madagascar	0	0	0	0	0	0	0	0

form the international commissions if members were required to travel too often and to too many different countries. To simplify certification, 2 groupings were therefore made of small numbers of countries, as follows: (1) Malawi, Mozambique, the United Republic of Tanzania, and Zambia; and (2) Botswana, Lesotho and Swaziland. The remaining 5 countries were dealt with separately. Angola, in particular, was a large country in which there had been serious civil disturbances both before and after it achieved independence in 1975 so that it was uncertain whether commission members would be able to travel extensively enough for certification to be possible. For this reason, a separate international commission was established for Angola so as not to prejudice the certification of any other country that might be grouped with it. The political problems associated with Namibia, South Africa and Southern Rhodesia have already been mentioned, while Madagascar, as an island, was a special case.

For the first time since certification in South America in 1973, the problem had to be faced that the variety of smallpox most recently present in some of these countries was mainly variola minor. In this situation, pockmark surveys, which had proved so useful in the countries of western and central Africa, were much less likely to reveal recent transmission of smallpox, because facial scars persisted in less than 10% of patients. To supplement such pockmark surveys as were performed, intensive surveillance for cases of chickenpox was carried out, and specimens were collected for laboratory examination—a procedure which reached its apogee in certification operations in the Horn of Africa (see Chapter 27). Surveillance for cases of chickenpox provided a measure of the sensitivity of the reporting system and permitted specimens to be collected from cases and outbreaks over a wide area. If cases had mistakenly been diagnosed as chickenpox instead of variola minor, this would be revealed by laboratory studies. Moreover, by obtaining material from outbreaks in which a patient had died, presumably of chickenpox, the likelihood of detecting smallpox, if it were present, was increased.

Time Schedules for Certification

Since there were so many countries for which certification was required by the end of 1979, all certification activities had to meet a strict time schedule. Further, if one of a group of neighbouring countries failed to achieve certification, none of the countries in that group could be certified. Various measures were taken to accelerate certification and maintain uniform progress—c. g., countries were requested to send information on the progress made in preparations for certification to the WHO Regional Office for Africa by cable every month. An example of such a request is reproduced below. Although formal communications were with the Regional Office, it was important that the epidemiologists in Nairobi and the Smallpox Eradication unit in Geneva should be kept informed of the situation; hence a copy of the cable was sent to each of them.

Outgoing cable:

"Reference progress SME [smallpox eradication] certification activities from now onwards please deliver to AFRO [Regional Office for Africa] a monthly cable to monitor status commission preparation including AAA cumulative totals pockmark surveys since surveys began BBB total number localities chosen for field surveys CCC total number localities visited by teams DDD total number of persons seen in schools or elsewhere EEE number of persons with facial pockmarks FFF number of specimens collected for laboratory study stop Please begin this cable report thirty October and forward thereafter on day thirty of subsequent months to AFRO with copy SME HQ [Smallpox Eradication unit] and ICP ES 005 [Epidemiological Surveillance of Diseases Intercountry Project] epidemiologists Nairobi and Maputo."

Malawi, Mozambique, United Republic of Tanzania, and Zambia

Precertification activities

These countries had recorded their last cases of smallpox between 1969 and 1971 (Table 26.1). Dr Ziaul Islam, a WHO epidemiologist based in Nairobi, who had worked on both the western and central African certification programmes, took the major role in precertification activities in this group of countries.

The preparation of country reports started early in 1977 while the certification of central Africa was in progress. In July 1977, a coordination meeting attended by WHO regional and Headquarters staff was held in Brazzaville, Congo, to assess progress. It was decided at this meeting that, in addition to pockmark surveys, a programme for the surveillance of chickenpox cases, with emphasis on the collection of specimens for laboratory examination, should have a high priority in the preparations for certification. It was proposed that at least 100 specimens from chickenpox patients should be collected in each country, from outbreaks separated in both space and time. By October 1977, Dr Islam had visited Malawi, the United Republic of Tanzania, and Zambia at least once to assist with the pockmark surveys and chickenpox surveillance. It was estimated that by December 1977 all the preparations for visits by an international commission would be completed.

Pockmark surveys. As part of the preparations for certification, pockmark surveys were carried out in each country, covering 3.2% of their combined population of 38.2 million (Table 26.2). No pockmarked children were seen among 70 621 children of preschool age, nor had any person with facial pockmarks suffered from smallpox later than 1970.

Chickenpox surveillance. In accordance with the decision made at the coordination meeting at Brazzaville in July 1977, all countries had collected a number of specimens from cases clinically diagnosed as chickenpox (Table 26.3). When examined at the WHO collaborating centres, no specimens showed poxvirus particles by electron microscopy and cultures for orthopoxviruses were uniformly negative. Herpesvirus particles were seen in 26% of the specimens.

Continued transmission in Malawi. During preparations for certification in Malawi, evidence was obtained which showed that smallpox transmission had continued for a long period of time without being recognized by the health services. The last reported case occurred in December 1969. In April 1972, Dr Islam discovered in a remote part of southern Malawi 48 individuals with facial pockmarks who had contracted their infections between April 1970 and February 1971—i.e., up to 14 months after the last reported case (see Chapter 20). Subsequently, during the precertification surveys, a joint Malawi–WHO team discovered a pockmarked girl and 2 other possible cases in the same area who gave a history of having been infected in September 1972. The exact status of these cases was never determined, but it was eventually concluded that, among the illiterate rural population, information given as to

Laboratory Diagnosis of Chickenpox

During precertification activities in many countries, large numbers of specimens from cases of chickenpox were submitted for laboratory testing to WHO collaborating centres. The varicella–zoster virus, which causes chickenpox, does not grow on the chorioallantoic membrane and grows only slowly in special kinds of cultured cells. However, typical enveloped herpes virions can be seen with the electron microscope in preparations made with fresh vesicular fluid (see Chapter 2, Plate 2.16).

Most reports from WHO collaborating centres showed a rather low percentage of sightings of herpes virions with the electron microscope in material that came from cases of chickenpox, compared with the very high percentage of positive results for pox virions from cases of smallpox. This is explained by the fact that the enveloped herpes virions are much more fragile than pox virions and often failed to survive intact during the process of shipment from the field to the laboratory.

Table 26.2. Malawi, Mozambique, United Republic of Tanzania, and Zambia: results of facial pockmark surveys conducted during precertification activities, 1977–1978

	Malawi	Mozambique[a]	United Republic of Tanzania	Zambia
Population, 1977 (millions)	5.5	10.6	17.0	5.1
Percentage of population seen	5.5	1.4	1.9	9.0
Number of preschool children examined	19 844	6 303	15 199	29 275
Number with pockmarks	0	0	0	0
Number of school-age children examined	242 068	69 543	206 021	364 194
Number with pockmarks[b]	737	161	1 242	1 261
Number of adults examined	42 050	70 908	97 058	65 763
Number with pockmarks[b]	179	523	657	301
Total number examined	303 962	146 754	318 278	459 332
Total number with pockmarks[b]	916	684	1 899	1 562

[a] In addition, in surveys carried out during the national mass vaccination campaign (June 1976–February 1978), 35 589 persons were found with facial pockmarks among 7 379 265 persons examined. None of them had contracted smallpox after 1969.
[b] Due to smallpox contracted before 1971.

Table 26.3. Malawi, Mozambique, United Republic of Tanzania, and Zambia: laboratory examination of specimens from cases clinically diagnosed as chickenpox, 1977–1978

Country	Number of specimens	Number positive for:		Number negative
		Poxvirus	Herpesvirus	
Malawi	319	0	62	257
Mozambique	65	0	20	45
United Republic of Tanzania	58	0	18	40
Zambia	86	0	36	50
Total	528	0	136	392

the year of illness was unreliable, and that the last case in Malawi had occurred in an outbreak that terminated spontaneously in 1971 without being detected by health staff.

Difficulties in precertification activities. WHO-assisted national smallpox eradication programmes had operated in Malawi, the United Republic of Tanzania, and Zambia, but the sensitivity of the surveillance system for smallpox had diminished in each of these countries since 1974. WHO had not been involved in smallpox eradication work in Mozambique. The precertification surveys just described were made possible only by detailing a WHO epidemiologist to work with designated national health workers in each country. Some logistic problems arose—e.g., in Mozambique, in which available resources were insufficient to permit the carrying out of a pockmark survey and extra funds had therefore to be provided to cover petrol costs and living allowances. Three new vehicles were also needed, but only for 2–3 months, so that it would have been wasteful to purchase them. Furthermore, they could not have been obtained in time, since procurement usually took 12 months. This problem was solved when the vehicles were made available by the WHO Expanded Programme on Immunization and money to cover local expenses was provided by WHO.

Visit by the International Commission, 6–29 March 1978

An International Commission for the Certification of Smallpox Eradication met in Maputo, Mozambique, from 6 to 9 March 1978. After reviewing the data from all 4 countries, the Commission set up 4 teams, one for each country, and reassembled for its final meeting in Lusaka, Zambia, 27 to 29 March.

After extensive travel throughout each country and examination of the reporting networks and of the data provided in the country reports, the Commission decided that, if smallpox transmission had continued after the date of the last known case, it would have been detected. The circumstances of the missed outbreak in Malawi were carefully scrutinized, but the epidemiological evidence indicated that the last case had occurred in 1971. The Commission noted that, even if the disease had persisted until September 1972, this was over 5 years ago, and the local situation had been examined in detail both by the joint Malawi-WHO team in precertification activities and by the Commission member during his visit. At its final plenary meeting in Lusaka the Commission agreed

WHO

Plate 26. 1. Participants in the final meeting of the International Commission for the Certification of Smallpox Eradication in Malawi, Mozambique, the United Republic of Tanzania and Zambia, held in Lusaka, Zambia, 29 March 1978. *Left to right:* I.H. Chu (WHO), A.H. Abou-Gareeb (WHO), **Z.M. Dlamini (Swaziland)**, I. Arita (WHO), **J. Moeti (Botswana), J.A. Espmark (Sweden), M. Davies (Sierra Leone)**, J.G. Breman (WHO), M. Altmann (WHO), P. Dordevic (WHO), I.D. Ladnyi (WHO), **F. Fenner (Australia)**, Z. Islam (WHO), C. Algan (WHO). The names of the Commission members are in bold type.

that the 4 countries should be certified to be free of smallpox.

Botswana, Lesotho and Swaziland

Coordination meeting

During the International Commission's visit to Lusaka in March 1978, mentioned above, a coordination meeting was held to discuss strategies for the certification of the remaining countries in southern Africa. It was attended by Dr Celal Algan and staff from the WHO Regional Office for Africa, Dr Joel Breman, formerly of the Center for Disease Control, Atlanta, USA, who had recently joined the Smallpox Eradication unit, and Arita. Apart from the Horn of Africa, where smallpox remained endemic until 1977, the last case in Africa had been reported in Botswana in November 1973. The small landlocked countries of Lesotho and Swaziland had experienced their last outbreaks in 1962 and 1966 respectively.

Although the 6 adjacent countries of Botswana, Lesotho, Namibia, South Africa, Southern Rhodesia and Swaziland formed an epidemiological unit (see Fig. 26.3), the coordination meeting decided that it would be very time-consuming and perhaps politically difficult to arrange for simultaneous precertification surveys and the certification of these countries by one or even several international commissions. Botswana was the only one of them in which WHO had been involved in a smallpox eradication programme when, after the outbreak there in 1971, a WHO team had assisted an augmented national programme. It was decided that arrangements should be made for the visit of an international commission to Botswana, Lesotho and Swaziland in March 1979, and that preparations for precertification activities in those 3 countries should begin immediately. Other measures were to be taken to obtain the information necessary to certify smallpox eradication in Namibia, South Africa and Southern Rhodesia (see below).

Table 26.4. Botswana, Lesotho and Swaziland: results of facial pockmark surveys conducted during precertification activities, 1978–1979

	Botswana	Lesotho	Swaziland
Population, 1978 (millions)	0.84	1.28	0.53
Percentage of population seen	19.7	18.5	14.1
Number of preschool children examined	16 654	24 541	3 790
Number with pockmarks	0	0	0
Number of school-age children examined	111 899	126 379	53 334
Number with pockmarks	6[a]	0	0
Number of adults examined	38 020	85 938	16 886
Number with pockmarks	99[a]	55[b]	2[b]
Total number examined	166 573	236 858	74 010
Total number with pockmarks	105[a]	55[b]	2[b]

[a] Due to smallpox contracted before 1974.
[b] Due to smallpox contracted before 1971.

Precertification activities

The last outbreak of smallpox in the region had been due to very mild variola minor in Botswana in 1971–1973 (see Chapter 20), and variola minor was the predominant variety of smallpox recently prevalent in South Africa, by which Lesotho was completely and Swaziland almost completely surrounded. However, outbreaks of variola major had occurred in all these countries in the past, and it was decided to carry out both pockmark surveys and chickenpox surveillance. Dr Moíses Altmann, a WHO epidemiologist stationed in Maputo, Mozambique, assisted the national health authorities in their preparations for the commission's visit. Progress was initially rather slow, but by January 1979 all 3 countries had prepared country reports and completed pockmark and chickenpox surveys.

Pockmark surveys. The pockmark surveys covered a large proportion of the small populations of the 3 countries (Table 26.4). No facial pockmarks were seen in 44 985 children of preschool age and only 6 cases (all in Botswana) were found among 291 612 schoolchildren. Pockmarks were somewhat more common in adults, being seen in 0.26% in Botswana and a smaller proportion in Lesotho and Swaziland, and heavy facial scarring was found only in adults, reflecting the outbreaks of variola major in the 1950s and 1960s.

Chickenpox surveillance. Specimens were collected from cases of chickenpox during precertification surveillance, care being taken to obtain specimens from as many separate outbreaks as possible. They were examined at WHO collaborating centres. None contained poxvirus, but herpesvirus particles were seen with the electron microscope in 28% of the specimens (Table 26.5).

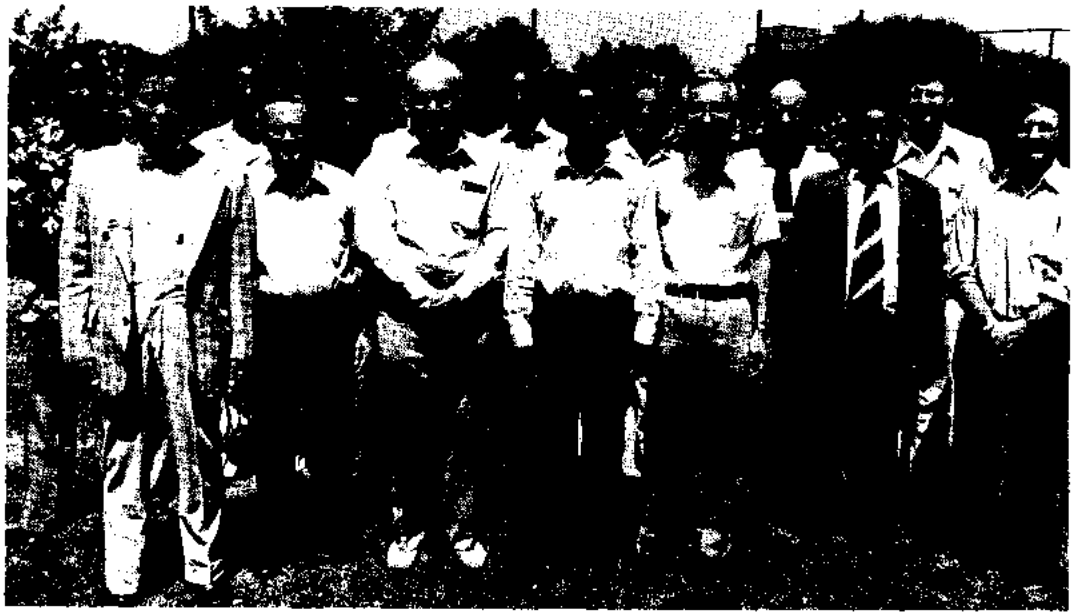
Table 26.5. Botswana, Lesotho and Swaziland: laboratory examination of specimens from cases clinically diagnosed as chickenpox, 1978–1979

Country	Number of specimens	Number positive for:		Number negative
		Poxvirus	Herpesvirus	
Botswana	260	0	75	185
Lesotho	58	0	17	41
Swaziland	41	0	9	32
Total	359	0	101	258

Visit by the International Commission, 5–23 March 1979

The first meeting of the International Commission was held in Gaborone, Botswana, from 5 to 7 March 1979. In addition to examining the country reports for these 3 countries, the Commission reviewed the data available at that time on smallpox eradication in the 3 neighbouring countries, Namibia, South Africa and Southern Rhodesia, because these 6 countries formed an epidemiological unit. The Commission then divided into 3 groups, which visited Botswana, Lesotho and Swaziland respectively, and reassembled for final discussions in Mbabane, Swaziland, between 21 and 23 March.

During their visits, Commission members themselves carried out pockmark and vaccination scar surveys, though necessarily on a much smaller scale than in the national



WHO

Plate 26.2. Participants in the briefing meeting of the International Commission for the Certification of Smallpox Eradication in Botswana, Lesotho, and Swaziland, held in Gaborone, Botswana, 7 March 1979. *Left to right, front row:* I.H. Chu (WHO), M. Altmann (WHO), **G. Meiklejohn (USA), W. Koinange (Kenya), I. Tagaya (Japan), D. Chilemba (Malawi), P.E.M. Fine (USA)**; *back row:* R.A. Ilbor (WHO), J.P. Sibiya (Botswana), L.T. Lesetedi (Botswana), V. Chinien (WHO), **A. Deria (Somalia)**, B.C. Dando (WHO), A. Sunde (Botswana), J.G. Breman (WHO). The names of the Commission members are in bold type.

surveys (Table 26.6). They discovered a higher proportion of pockmarked schoolchildren and adults than had been found in the national surveys in Botswana and Swaziland, but fewer in Lesotho. In any case, even these higher frequencies were quite low (0.26% and 0.29% in schoolchildren in Botswana and Swaziland respectively) and no pockmarked children under the age of 6 were found, out of a total of 2533 examined.

There was some doubt among Commission members in Botswana whether smallpox transmission there had been interrupted in 1973 or had extended into 1974. Two suspected cases of smallpox in children had occurred in 1974, but it was impossible to confirm or disprove the diagnosis.

The vaccination scar survey conducted by Commission members revealed a high vaccination coverage of the population in all 3 countries; in the age group under 15 years, for example, it was 96% in Botswana, 85% in Swaziland and 72% in Lesotho. In Botswana, refugees, bushmen and a religious sect whose

Table 26.6. Botswana, Lesotho and Swaziland: results of facial pockmark surveys carried out by members of the International Commission in March 1979

	Botswana	Lesotho	Swaziland
Number of preschool children examined	1 766	218	549
Number with pockmarks	0	0	0
Number of school-age children examined	23 978	12 241	12 562
Number with pockmarks	62[a]	0	36[b]
Number of adults examined	4 486	2 770	1 811
Number with pockmarks	22[a]	2[b]	11[b]
Total number examined	30 230	15 229	14 922
Total number with pockmarks	84[a]	2[b]	47[b]

[a] Due to smallpox contracted before 1974.
[b] Due to smallpox contracted before 1971.

members objected to vaccination on principle were considered as high-risk groups among whom the transmission of smallpox was more likely to continue. However, national vaccination surveys and visits by Commission members showed satisfactory vaccination coverage in each of these groups.

Because the variety of smallpox most recently prevalent in these 3 countries had been variola minor, the absence of pockmarks in children was less significant than in the majority of other countries, but the absence of variola virus in specimens taken from cases diagnosed as chickenpox and the high level of vaccinial immunity were persuasive. Noting that there had been no evidence of confirmed smallpox since 1973 or of suspected cases since 1974, the Commission certified that smallpox had been eradicated from Botswana, Lesotho and Swaziland.

South Africa

With a population of 22.8 million in 1970, South Africa was the most populous country in southern Africa. Variola major and variola minor had been endemic up to the Second World War, but thereafter only variola minor had persisted as an endemic disease, and was not regarded very seriously by the health authorities. Apart from a visit to South Africa in 1972 by Henderson (see Chapter 20), the country had had no contact with the WHO smallpox eradication campaign and had not established a national smallpox eradication programme. Smallpox was regarded as one of the diseases for which vaccination should be provided, but was considered to be of minor importance compared with poliomyelitis, measles, diphtheria, and other diseases.

Arrangements for certification

Following the Consultation on the Worldwide Certification of Smallpox Eradication in October 1977, the Director-General of WHO wrote to the South African Minister of Health and Welfare to propose that the South African government should participate in the global certification of smallpox eradication. In his letter he suggested that a visit early in 1978 by Fenner, who had been the chairman of the Consultation, would be a useful way to begin this activity. Within 10 days of the dispatch of this letter, South Africa informed WHO by cable of its willingness to participate in these certification activities and to provide every assistance during Fenner's visit.

Visit by Fenner, 19 January–19 February 1978. The purpose of the visit was threefold: (1) to advise South African health officials on how to prepare a country report for submission to the Global Commission; (2) to emphasize the importance of chickenpox surveillance and make arrangements for the collection of specimens for laboratory examination by WHO collaborating centres; and (3) to obtain an impression of the recent history of smallpox and rural health services in South Africa (including some of the "black homelands"). Fenner's itinerary is shown in Fig. 26.4. With the help of the South African government, the trip was extended to include Namibia (see below). He was cordially received by government and provincial health officials (see box) and visited infectious disease hospitals, university medical schools, diagnostic laboratories in Johannesburg and Cape Town, and rural health centres in northern Transvaal and 3 of the "black homelands", Bophuthatswana, Lebowa and Transkei.

The laboratory services were found to be of high quality and a network of diagnostic laboratories covered most of the country. However, their practice of testing for ortho-

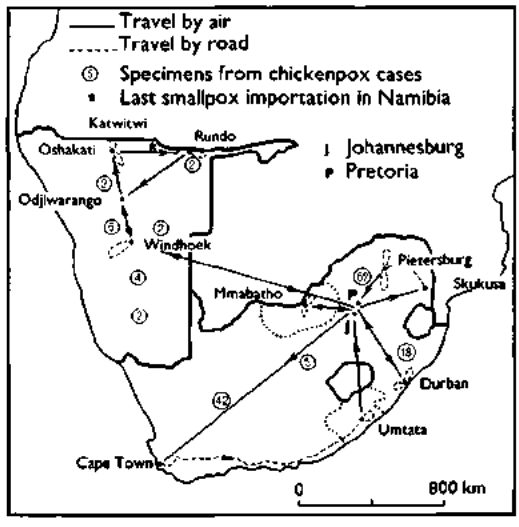


Fig. 26.4. Itinerary of the visit to South Africa and Namibia by the chairman of the Global Commission, Dr F. Fenner, 19 January – 19 February 1978, and numbers of specimens from cases of chickenpox from each of the provinces of South Africa and various parts of Namibia.

Collaboration between South Africa and WHO on Smallpox Eradication

The following note prepared by Fenner on his return from South Africa illustrates that country's willingness to cooperate with WHO's global certification activities:

"Everywhere I went I was received with great cordiality, and there were frequent expressions of satisfaction that WHO had arranged the visit. No effort was spared to enable me to see what I regarded as the 'vulnerable' areas, the more heavily populated parts of Namibia near the Angolan border and the northern parts of Transvaal (Lebowa) and Bophuthatswana, near Botswana.

"I was driven around the countryside and to clinics and hospitals by senior health officials, health inspectors or nursing sisters over a distance of more than 3000 km, and a chartered plane was made available for 3 days. Such travel afforded opportunities for extensive informal discussion of the health conditions and the complex politics of these parts of Africa, as well as observation of the countryside and living conditions in the rural areas, and the rural hospitals and clinics."

poxviruses by growth in tissue culture rather than on the chorioallantoic membrane, and reporting positive results as indicating a "member of the vaccinia–variola group" was confusing (see Chapter 20). Variola virus stocks were held in the National Institute for Virology, but the South African Director-General of Health would not agree to a request by Fenner that they should either be transferred to a WHO collaborating centre or destroyed. In fact, it was not until December 1983 that they were finally destroyed (see Chapter 28).

Vaccine was produced in a laboratory in Cape Town for use locally and in some neighbouring countries—e.g., Southern Rhodesia. Tests on freeze-dried vaccine carried out in 1970 by the WHO Collaborating Centre for Smallpox Vaccine in Bilthoven, Netherlands, showed that it met WHO standards.

Preparation of the country report. It was suggested that South Africa should submit its country report by 1 June 1978 and complete the chickenpox survey in October 1978, so that the situation could be reviewed at the Global Commission meeting in December 1978. However, when no material had arrived by 12 September, Arita sent a cable to Pretoria requesting the submission of a country report documenting smallpox eradication as soon as possible. To avoid further delay, Fenner revisited South Africa briefly in mid-October, and Dr Nicole Grasset, formerly the regional smallpox adviser in the WHO South-East Asia Region, who had lived in South Africa in her youth, visited the country in November and brought data and a draft report back to Geneva, where it was finalized by staff of the Smallpox Eradication unit.

The delay in sending the results of the chickenpox surveys was due to the seasonal character of the disease; outbreaks occur in spring and, in the Southern Hemisphere, this starts in September, so that, by October, there had been too few to enable the stipulated 100 specimens to be collected.

Review of country report by the Global Commission, December 1978

The country report and the results of an incomplete chickenpox survey were presented to the Global Commission at its meeting in Geneva from 4 to 7 December 1978. The Commission noted that South Africa had relatively well developed health services, as shown by the overall doctor to population ratio of 1:1806 and registered nurse to population ratio of 1:573. In addition, 5660 health stations were responsible for reporting communicable diseases. After the last known outbreak in 1971, when special efforts were made to achieve high vaccination rates in the northern Transvaal (see Chapter 20), smallpox vaccination was being performed as part of a well-organized immunization programme which also provided poliomyelitis, BCG and diphtheria–pertussis–tetanus vaccination.

The results of facial pockmark and vaccination scar surveys carried out in widely separated rural and urban areas during 1978 are shown in Table 26.7. An additional survey of 17 064 children under 15 in Bophuthatswana and Transkei revealed none with facial pock-

Table 26.7. South Africa: results of facial pockmark and vaccination scar surveys in 1978, by age group and type of locality

Age group (years)	Localities	Persons examined		
		Total number	Number with facial pockmarks	Percentage with vaccination scar
0–5	Urban centres	3 170	0	82.3
	Rural ("black homelands")	10 685	0	68.8
6–15	Urban centres	1 051	0	86.7
	Rural (provinces)	271 191	0	86.2
	Rural ("black homelands")	36 391	0	80.7
>15	Urban centres	11 011	4[a]	69.5

[a] Due to smallpox contracted many years earlier.

Table 26.8. South Africa: results of examination by WHO collaborating centres of specimens collected from cases clinically diagnosed as chickenpox

Province	Number of specimens examined	Number positive for:		Number negative
		Poxvirus	Herpesvirus	
Cape	42	0	9	33
Natal	18	0	5	13
Orange Free State	5	0	3	2
Transvaal	62	0	25	37
Total	127	0	42	85

marks and 67.6% with vaccination scars. Four adults with facial pockmarks gave histories of attacks of variola major many years earlier.

When the Global Commission met in December 1978, no data were available on the laboratory examination of specimens from cases of chickenpox, and it was therefore decided to delay certification pending the arrival of the results of this survey. By June 1979, 127 specimens had been submitted for examination, the majority coming from the northern Transvaal (see Fig. 26.4), where the last outbreak of smallpox had occurred in 1971. All were negative for poxvirus, but herpesvirus particles were seen in 33% of the specimens (Table 26.8).

After receipt of the results of the examination of the first 100 specimens, Arita wrote to members of the Global Commission, who, on the basis of their review of the situation in December 1978 and the results of the chickenpox survey, agreed on 17 April 1979 that smallpox eradication had been achieved in South Africa.

Namibia

Although the United Nations had terminated the South African mandate over Namibia in 1966 and the South African presence there had been declared illegal by the International Court of Justice in 1971, the country was in fact controlled and administered by South Africa, under the name "South West Africa". In this sparsely populated country, the highest population density being 7.5 persons per square kilometre in Ovamboland, adjacent to the border with Angola, endemic smallpox was said never to have been present, though there had been occasional importations from Angola, most recently in 1956. Endemic smallpox had been eliminated from Angola in 1959 (see below) and although cases had occurred as recently as 1973 in Botswana, these were in the eastern part of that country, separated from Namibia by the Kalahari desert. The South African Institute for Medical Research operated a branch laboratory in Windhoek, the capital, and small laboratories in some other towns in Namibia.

Visit by Fenner, 5–9 February 1978

During his trip to South Africa early in 1978, Fenner also spent 5 days in Namibia (see Fig. 26.4). He met health officers and staff in hospitals and laboratories, obtained information on health services, especially the surveillance and control of communicable diseases, visited schools and conducted a limited vaccination scar survey. After his departure, a country report was prepared by the South African health authorities and sent to the Global Commission.

Review of the country report by the Global Commission, December 1978

The country report was considered at the meeting of the Global Commission in December 1978. It followed the usual lines, describing the geography and demography,

health administration, history of smallpox and records of vaccination activities. Between 1969 and 1978, 10 specimens had been examined for suspected smallpox at the National Institute for Virology in Sandringham; all were negative. Pockmark and vaccination scar surveys had been conducted throughout the country in April–November 1978 (Table 26.9). The 3 pockmarked adults found were Angolans who said that they had suffered from smallpox in childhood.

During 1978 and 1979, 18 specimens collected from cases clinically diagnosed as chickenpox (see Fig. 26.4) were examined in a WHO collaborating centre; none contained poxvirus but 9 showed herpesvirus particles.

On the basis of the history of smallpox in Namibia, the low probability of importations from adjacent countries during the previous decade, the results of the facial pockmark surveys and the high vaccination rate in individuals over 5 years of age, the Global Commission certified that smallpox had been eliminated from Namibia.

Southern Rhodesia (Zimbabwe)

Southern Rhodesia was a British colony until 1980, when it attained independence and was renamed Zimbabwe. In 1965 the white colonists had made a unilateral declaration of independence and since then the country had been in a state of civil war. Legally, in 1978, it remained under the jurisdiction of the United Nations Sanctions Committee. In order to obtain information on the smallpox situation, the Director-General of WHO wrote to the Southern Rhodesian authorities requesting that 2 WHO consultants should be allowed to visit the country to assess whether smallpox had been eliminated. A favourable reply having been received, Dr Nicole Grasset and Dr Gordon Meiklejohn, both highly experienced in smallpox eradication activities, visited the country in January 1978.

Visit by Dr Grasset and Dr Meiklejohn, 10–30 January 1978

Since Southern Rhodesia was a much smaller country, the objectives of this visit differed from those of Fenner's visit, mentioned above, to South Africa and Namibia. The consultants' aim was to obtain enough information, by travel and inquiry, and supported by subsequent investigations by local personnel, to be able to submit to the Global Commission a definitive report on the smallpox situation in Southern Rhodesia.

The consultants were warmly received by the local authorities (see box) and after initial consultations in Salisbury (Harare), they travelled separately around the 5 provinces, carrying out extensive pockmark and vaccination scar surveys as well as evaluating the level of surveillance of infectious diseases by health personnel. Subsequently, national health personnel carried out further and more extensive studies. The consolidated results of all these surveys are shown in Table 26.10.

In their inquiries, the consultants observed that there was a remarkable lack of knowledge about smallpox among persons under 25 years of age. Almost without exception they failed to recognize the smallpox pictures on the recognition cards and stated that they had never seen or known of the presence of the disease. On the other hand, many older persons knew about smallpox from their childhood, and 0.26% of adults surveyed had facial pockmarks, the most recent being said to date from an illness in 1966.

In addition to their field survey, the consultants commented on the health services, which they described as extensive, well

Table 26.9. Namibia: results of facial pockmark and vaccination scar surveys in April–November 1978, by age group

Age group (years)	Persons examined		
	Total number	Number with facial pockmarks	Percentage with vaccination scar
0–5	1 260	0	56.9
6–15	27 913	0	92.5
>15	2 983	3[a]	83.0

[a] Angolans who had had smallpox in childhood.

Table 26.10. Southern Rhodesia: results of facial pockmark and vaccination scar surveys in January–April 1978, by age group

Age group (years)	Persons examined		
	Total number	Number with facial pockmarks	Percentage with vaccination scar
0–6	49 401	0	79.0
7–14	39 835	4[a]	95.0
>14	26 872	70[a]	94.2

[a] Due to smallpox contracted before 1967.

Attitude of the Southern Rhodesian Authorities to the Visit by WHO Consultants

Dr Grasset reported as follows: "Dr G. Meiklejohn and myself were everywhere received with great cordiality and everything was done to facilitate our work in Rhodesia ... Maps, charts and tables concerning the smallpox programme in Rhodesia since 1954 were given to us, and the smallpox activities and other health programmes were freely discussed.

"... In order to carry out surveys in as many localities as possible, half the country's territory was covered by Dr Meiklejohn and the other half by myself ... The Chief Health Inspector accompanied Dr Meiklejohn throughout his travels, and I was escorted by different European and African provincial health officials.

"As the majority of localities we had to visit for epidemiological reasons were in areas bordering Mozambique, Zambia and Botswana, where few or no civilians travel due to civil warfare, special arrangements were made to bring us as near as possible to the villages by chartered or government four-seater planes. From the rough air strips, we were usually provided with a metal-protected lorry accompanied by armed African soldiers. In particularly dangerous areas, two military jeeps with soldiers escorted us throughout the day and soldiers were placed on the airstrips to assure our security at the departure of the charter plane.

"As every day we had to examine a few thousand children in one to four localities, advance planning was made by the authorities, i.e., the population was grouped at gathering points, and up to 8 African health assistants were made available to assist us in our work.

"On no occasion was any information requested kept from us."

planned and supported by excellent communications. There was a medical school in Salisbury; the health personnel included many European nurses and physicians, a large proportion of whom had undergone training in public health and tropical medicine; and an extensive network of 83 mission hospitals existed. Because of the civil war, health staff were working under extremely difficult circumstances, often at the risk of personal injury or death. Although smallpox was at the top of the list of notifiable diseases, the country had never set up a separate smallpox eradication programme. Mobile vaccination teams sought to vaccinate the entire population against smallpox in a 3-year cycle, using liquid smallpox vaccine purchased from South Africa. There were no systematic search operations and, apart from reporting during an outbreak, no routine "nil" reports. Reliance was placed on the extensive and well-distributed network of health units and on the alertness of staff in high-risk areas. This approach appeared to have been reasonably successful in detecting almost all outbreaks, and transmission was interrupted in 1970. The instability in some border areas raised doubts as to the ability of this health structure to detect outbreaks rapidly in those areas if there should be an importation, but the neighbouring countries—Botswana, Mozambique, South Africa and Zambia—had been free of smallpox since 1973 or earlier.

The consultants found no evidence of smallpox transmission within Southern Rhodesia or of importations since the last reported outbreak there in 1970. It was their opinion that, because the health units were numerous, geographically well distributed and staffed with well-trained and alert personnel, any case of smallpox that might have occurred after 1970 would have been detected. Facilities for laboratory diagnosis, including electron microscopy, were available in Salisbury and many specimens had been tested between 1970 and 1977, all with negative results. After the consultants' visit, a further 23 specimens obtained from patients with what was diagnosed clinically as chickenpox were examined in a WHO collaborating centre. Herpesvirus particles were found in 10 of them but poxvirus in none.

Review by the Global Commission, December 1978

At its meeting in December 1978 the Global Commission reviewed the consultants' report and the results of the pockmark and

vaccination scar survey supplied by the government, and certified that Southern Rhodesia was free of smallpox.

Angola

The only countries remaining for assessment in southern Africa were Angola and the island of Madagascar. At the coordination meeting held in Lusaka in March 1978, it had been decided that the certification of Angola should be carried out by an international commission in February 1979.

The last reported cases of smallpox in Angola had occurred in 1966. Although the country had suffered from political instability since 1961, there had been a good vaccination programme, in which freeze-dried vaccine had been used, until 1975. Variola minor was endemic up to 1959, and outbreaks of variola major had occurred following importations from Zaire during the 1960s, the last taking place in 1966. Each of these was investigated by state epidemiologists and confirmed by virus isolation at a laboratory in Luanda. The extensive national vaccination campaign extended through 1974 but was then sharply curtailed because of the civil war, which culminated in national independence in 1975. By then, more than 3 years had elapsed since the last outbreak in Zaire, which had been the source of earlier importations. However, in 1978 many areas were regarded as inaccessible and it was thought that it would be difficult to carry out pockmark surveys and obtain specimens from cases of chickenpox in those parts of the country.

Precertification activities

Dr Joel Breman of the Smallpox Eradication unit helped to plan the precertification programme and Dr René F. M. Collas, a WHO epidemiologist, and Mr José F. Verani, a WHO technical officer, who were stationed in Angola in connection with other WHO projects, assisted the national health officials. In August 1978 Dr Clovis H. Tigre, a Brazilian epidemiologist, visited Angola to review the progress of field surveys and the preparation of the country report. He found that little had been done.

In November 1978, at Arita's request, Dr Francisco J. C. Cambournac, a former resident of Angola who had been Director of the WHO Regional Office for Africa but had retired to Portugal, provided valuable data on smallpox in Angola before 1975, the year of independence. The country report was finally prepared later that month, by which time 79 specimens had been collected from chickenpox patients. However, the field survey had been delayed because of poor communications and lack of resources, and it was doubtful whether all the data would be available for the visit of the International Commission scheduled for February 1979. Early in December, after a meeting at the Ministry of Health between government officials and the WHO programme coordinator in the country, the survey proceeded more rapidly and by early January 1979 all preparations had been completed.

Pockmark survey. The pockmark survey carried out by the national health authorities covered all the provinces (Fig. 26.5) and 11% of the total population. About 0.8% of the adult population and 0.04% of school-age children had facial pockmarks, but only 1 pockmarked child was found in the preschool age group (Table 26.11), and it was decided that the scarring had been caused by chickenpox.

Chickenpox surveillance. Variola minor had virtually replaced variola major in Angola in

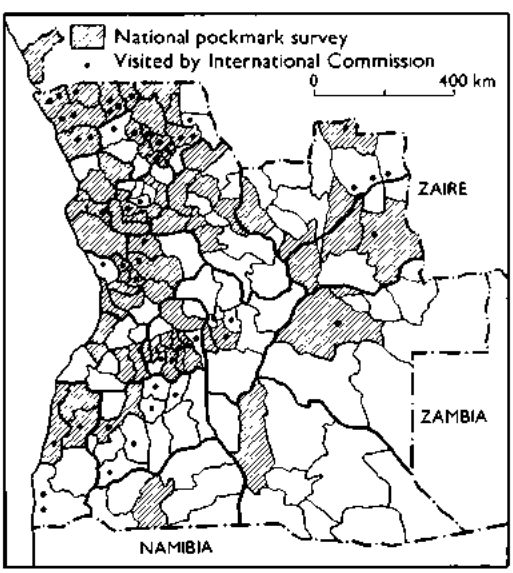


Fig. 26.5. Certification activities in Angola: municipalities covered by the national pockmark survey, July–December 1978, and those visited by members of the International Commission for the Certification of Smallpox Eradication in Angola, 5–16 February 1979.

Table 26.11. Angola: results of facial pockmark survey in July–December 1978, by age group

Age group	Persons examined		
	Total number	With facial pockmarks	
		Number	%
Preschool children	81 572	1[a]	0
School-age children	444 401	177[b]	0.04
Adults	218 454	1 807[b]	0.83

[a] One child had facial scarring which resembled pockmarks caused by smallpox, but after further examination it was decided that the scarring had been caused by chickenpox.
[b] Due to smallpox contracted before 1974.

the 1950s and had been present together with variola major in neighbouring countries (Zaire and Zambia) until the late 1960s. A total of 122 specimens collected from outbreaks of chickenpox occurring in various provinces (Fig. 26.6) were examined in a WHO collaborating centre; none contained poxvirus but 12 were found to contain herpesvirus particles. This unusually small proportion of herpesvirus-positive specimens was due to a breakdown of the electron microscope during the period concerned, so that much of the material had only been cultured.

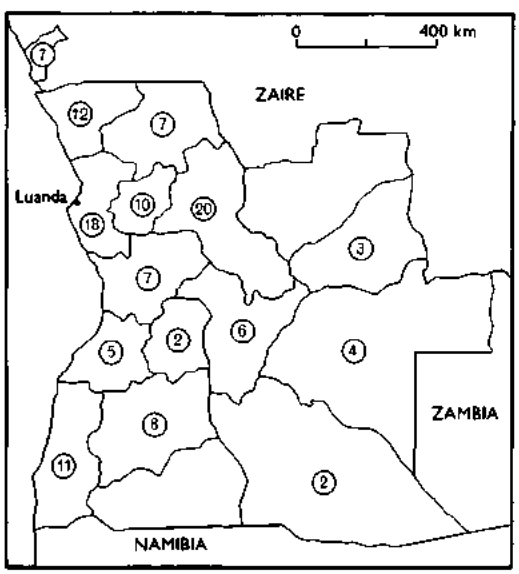


Fig. 26.6. Numbers of specimens collected from chickenpox cases in various provinces of Angola between July 1978 and February 1979.

Visit of the International Commission, 5–16 February 1979

After reviewing the data supplied by the Angolan authorities in Luanda, the Commission formed 5 teams, which travelled widely throughout the country (see Fig. 26.5) before meeting again in Luanda on 15 and 16 February to review the situation. Contrary to the opinion prevailing earlier, members were able to visit most parts of Angola, except the south-east, which bordered on Namibia, a country that had been free of smallpox for decades. During their visits they conducted a facial pockmark survey that covered 28 167 persons, of whom 495 had pockmarks; these were all persons of school age or older and all had contracted the illness causing the pockmarks prior to 1966.

Between 1966 and 1974 there had been a good vaccination programme, 1.5–2.8 million people out of a population (in 1974) of about 6.3 million having been vaccinated annually with freeze-dried vaccine of good quality purchased from a number of European countries. There were 144 reporting units in the 16 provinces and, on average, one-third of them were sending in monthly epidemiological reports. Taking into consideration the absence of smallpox from Angola since 1966 and from neighbouring countries since the late 1960s, the field investigations carried out by the Angolan authorities, and the results of the chickenpox survey, the International Commission certified Angola to be free of smallpox.

Madagascar

Because Madagascar was an island with a relatively small population, it had been possible to interrupt smallpox transmission there during the First World War, and to control effectively the few importations that occurred between 1925 and 1931 (see Chapter 8). The Consultation on the Worldwide Certification of Smallpox Eradication, meeting in October 1977, decided that all that was needed from Madagascar was a country report, which was presented by the government to WHO in December 1977.

An unusual feature of this report was the large number of recorded deaths from chickenpox (Table 26.12). The data for 1972–1975 were supplied in the country report, the other figures by correspondence. These data could

Table 26.12. Madagascar: number of reported cases of and deaths from chickenpox, 1972–1978

Year	Number of cases	Number of deaths	
		Original figures[a]	Revised figures[b]
1972	11 069	7	7
1973	19 408	26	26
1974	27 322	187	8
1975	33 076	108	5
1976	22 213	97	11
1977	18 557	6	6
1978	20 204	20	20

[a] From the Ministry of Health of Madagascar.
[b] After investigations by Dr Z. Islam in March 1979.

have been interpreted as the result of an unrecognized importation of variola major into Madagascar in 1974 and its subsequent spread and misdiagnosis as chickenpox during 1975 and 1976. The likelihood that this was so was increased when the data by province for 1976 showed that the case-fatality rate for "chickenpox" in the province of Antananarivo was almost 1% (8572 cases; 83 deaths). Correspondence between the Smallpox Eradication unit and health officials and the WHO programme coordinator in Madagascar failed to elicit a satisfactory explanation for the reported high death rates from chickenpox, and in December 1978 the Global Commission deferred certification pending the provision of further information.

It was arranged that Dr Ziaul Islam should visit Madagascar and investigate the situation. Working there from 26 February to 9 March 1979, he checked the original records for 1972–1978 and discovered that measles deaths had sometimes been attributed to chickenpox, typing errors had been made, and confusion had resulted from using reporting forms for mortality when those intended for reporting morbidity had run out; sometimes no explanation for the figure reported could be found. His final assessment of the numbers of deaths from chickenpox, also shown in Table 26.12, is consistent with the occurrence of chickenpox only.

Dr Islam's report, which also provided some additional information on the health structure and vaccination programme in Madagascar, was distributed to members of the Global Commission on 10 May 1979. They accepted the explanation that the high mortality attributed to chickenpox was due to reporting and/or recording errors and eradication in Madagascar was certified by correspondence on 29 June 1979. Had the Global Commission not made such a decision, arrangements between the Smallpox Eradication unit and the government of Madagascar were in hand to carry out an intensive pockmark survey in the areas in which large numbers of chickenpox deaths had been originally reported, but this did not prove necessary.

UGANDA AND THE SUDAN

In parallel with the certification activities in the countries of southern Africa, arrangements were made for international commissions to visit the 2 African countries (other than those of the Horn of Africa) for which certification was still required—namely, Uganda and the Sudan. Uganda had reported its last endemic case of smallpox in

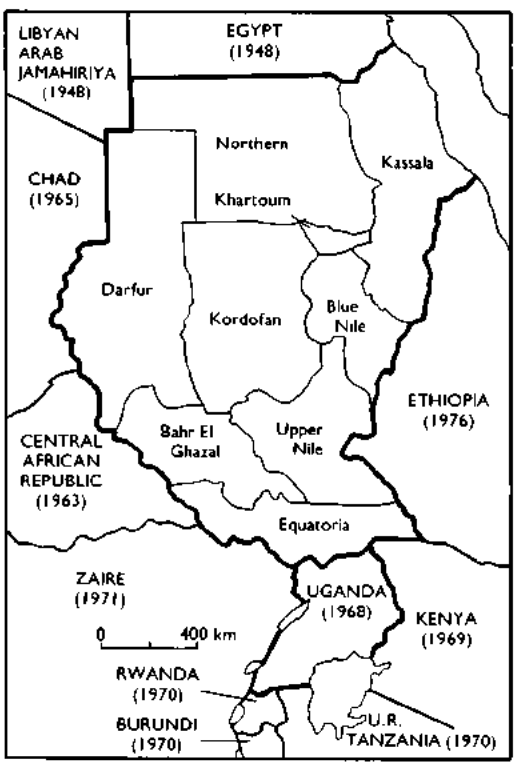


Fig. 26.7. Sudan and Uganda, showing the provinces of the Sudan at the time of the precertification activities and the years in which smallpox ceased to be endemic in neighbouring countries. Uganda was visited by an international commission from 11 to 27 October 1978 and the Sudan by another international commission from 15 to 29 November 1978.

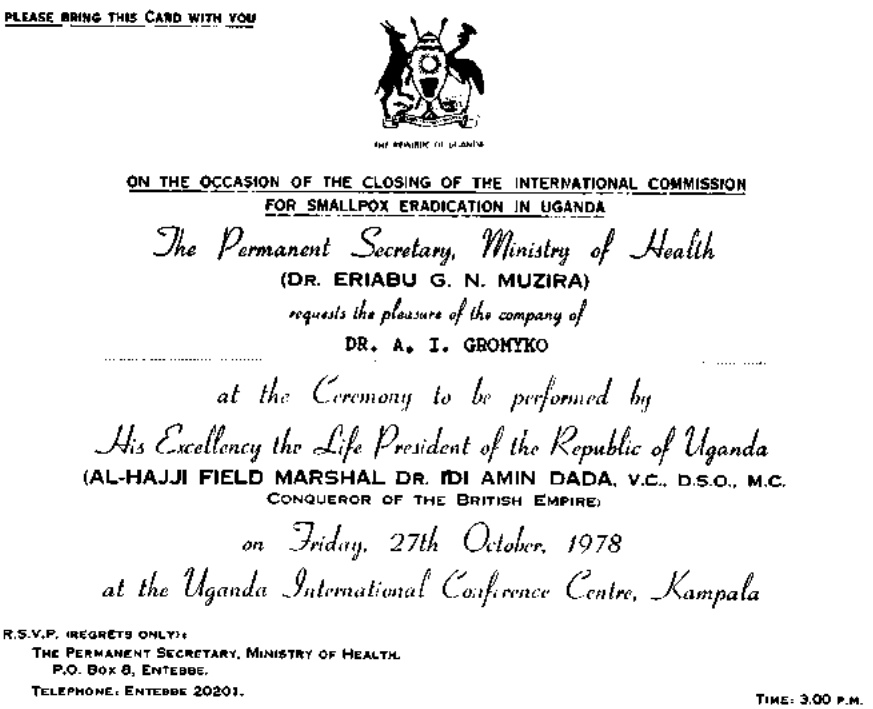
1968, but imported cases had occurred each year between 1969 and 1972, originating from the neighbouring Equatoria Province of the southern Sudan (Fig. 26.7), in which there had been civil disturbances until 1972. The certification of eradication in Uganda was therefore dependent on that in the Sudan. However, certification could not be undertaken in the Sudan until 1978 because of the risk of importations from Ethiopia, in which smallpox remained endemic until August 1976. Plans were therefore made for the certification of the Sudan and Uganda in October–November 1978, by separate international commissions.

Uganda

Precertification activities

Preparations for certification in Uganda followed the pattern that had been developed in western Africa, where a similar long interval had occurred between the last reported case and certification (see Chapter 25). Dr Chu In Ho, a WHO epidemiologist stationed in Kampala, assisted the Ugandan health authorities in the preparation of the country report and in conducting pockmark surveys and chickenpox surveillance. For the pockmark survey (Table 26.13), 622 localities widely dispersed over Uganda's 10 provinces were selected and over 1.5 million persons, representing 12.2% of the total population of Uganda, were examined. Most of the more recent outbreaks of smallpox in Uganda had been due to variola minor (see Chapters 8 and 19), so it was not surprising that facial pockmarks were rare, being found in only 0.005% of persons of school age or older. None was ascribed to smallpox infection contracted after 1970.

A WHO-supported virus laboratory in Entebbe had confirmed diagnoses of smallpox in 1970 and 1972, but thereafter had gradually ceased to function. In preparation for



PLEASE BRING THIS CARD WITH YOU

ON THE OCCASION OF THE CLOSING OF THE INTERNATIONAL COMMISSION FOR SMALLPOX ERADICATION IN UGANDA

The Permanent Secretary, Ministry of Health

(DR. ERIABU G. N. MUZIRA)

requests the pleasure of the company of

DR. A. I. GROMYKO

at the Ceremony to be performed by

His Excellency the Life President of the Republic of Uganda

(AL-HAJJI FIELD MARSHAL DR. IDI AMIN DADA, V.C., D.S.O., M.C.
CONQUEROR OF THE BRITISH EMPIRE)

on Friday, 27th October, 1978

at the Uganda International Conference Centre, Kampala

R.S.V.P. (REGRETS ONLY):
THE PERMANENT SECRETARY, MINISTRY OF HEALTH,
P.O. BOX 8, ENTEBBE.
TELEPHONE: ENTEBBE 20201.

TIME: 3.00 P.M.

Plate 26.3. The President of Uganda took a personal interest in the certification of smallpox eradication in his country. The eradication programme transcended personal and political barriers in a global effort towards a common goal.

Table 26.13. Uganda: results of facial pockmark surveys by national authorities, April–September 1978, and by International Commission members, October 1978, by age group

Age group	Survey	Number of persons examined	
		Total	With facial pockmarks
Preschool children	National	85 504	0
	International Commission	4 932	0
School-age children	National	900 115	47[a]
	International Commission	25 926	11[a]
Adults	National	572 266	19[a]
	International Commission	29 629	2[a]

[a] Due to smallpox contracted before 1971.

certification, 118 specimens were collected from cases of chickenpox occurring in all provinces during the period April–September 1978. On examination at WHO collaborating centres, none was found to contain poxvirus particles.

Visit of the International Commission, 11–27 October 1978

After an initial 3-day meeting in Kampala, the Commission was divided into 3 teams, which between them visited all the provinces. As well as inspecting health units and the reporting system, they carried out facial pockmark surveys (see Table 26.13) which confirmed the results of the larger national survey.

Before certifying that smallpox transmission had been interrupted in Uganda, members of the Commission made a special visit to the Virus Research Institute in Entebbe and confirmed that all stocks of variola virus previously held there had been destroyed on 27 July 1976, after receipt of the letter dispatched from the Smallpox Eradication unit earlier that month (see Chapter 30).

Sudan

A WHO-assisted smallpox eradication programme had been carried out in the Sudan, geographically the largest country in Africa, from 1969 onwards but was not very effective until 1972 (see Chapter 18). The last endemic case of smallpox had occurred in Bahr El Ghazal Province in December 1972. The requisite 2-year surveillance period after the last known case had been completed by the end of 1974, but the eradication of smallpox was not certified in the Sudan by an international commission until November 1978.

Certification was delayed because the Sudan was at the crossroads of movements by seasonal agricultural workers and pilgrims, some of whom came from western Africa on their way to Mecca, and some from Ethiopia, in which smallpox had been endemic until 1976 (see Chapter 18, Fig. 18.6). The movement of refugees from Ethiopia into the southern Sudan also caused problems. The certification of smallpox eradication in the Sudan could be undertaken with confidence only after transmission had been interrupted in Ethiopia.

The delay in certification caused considerable problems for the Sudanese health authorities, since they had to maintain surveillance for a further 5 years after the last case. However, the fact that they had done so meant that smallpox eradication in the central and eastern parts of the African continent could be certified with much greater confidence. In addition to Ethiopia, the Sudan had borders with the Central African Republic, Chad, Kenya, Uganda and Zaire, from which cases had regularly been imported in the 1950s and 1960s. The absence of importations from these countries into the Sudan between 1972 and 1978 provided additional assurance that transmission had ceased in these countries as well.

Precertification activities

After the last case occurred in December 1972, surveillance continued in the Sudan, more than 600 staff being employed for the purpose, including 48 supervisors, 18 assessors and 369 vaccinators, who were distributed throughout the 13 provinces. During this period 1 or 2 WHO epidemiologists or consultants assisted in developing and implementing surveillance. The smallpox eradication staff who contributed in this way included Dr Abdel Hamid el Sayed, as the national director of the programme, and the WHO epidemiologists Mr David Bassett, Dr Donald P. Francis and Dr Satnam Singh.

While the reporting system was being strengthened, programme staff conducted a

systematic search for hidden foci of smallpox, particularly in the southern provinces and the areas bordering on Ethiopia. Active searches were conducted in villages, health establishments, schools, police stations and markets to seek information on cases of diseases with a rash, and a reward was offered. The vaccination programme was also maintained.

Pockmark survey. Between 1975 and 1977 smallpox eradication programme staff examined a total of nearly 2 million persons, out of a total population of 14 million, for facial pockmarks (Table 26.14). The few people found with them (0.04% of those examined, all of school age or older) had contracted smallpox before 1972.

Chickenpox surveillance. Because of possible diagnostic confusion between variola minor and chickenpox, the latter was made a notifiable disease and, wherever possible, outbreaks were investigated by smallpox eradication programme staff. Between 1973 and 1977, 17 690 cases, including 10 deaths, were reported (Table 26.15). Each year, specimens for laboratory investigation were taken from a number of cases, usually those with unusual features. Of 74 specimens examined in WHO collaborating centres none contained poxvirus.

Special searches in the southern provinces. Because of the difficulties of access before 1972, special searches were conducted in Upper Nile and Equatoria Provinces. During two searches in Upper Nile, in 1972 and 1974, 718 000 out of 798 000 inhabitants of the province were vaccinated. A vaccination scar survey revealed a coverage of 85% in the age group 0–4 years and 98% in the age group 5–14 years.

In Equatoria Province, the special surveillance team operating in January 1974 dis-

Table 26.14. Sudan: results of facial pockmark surveys conducted by smallpox eradication programme staff between 1975 and 1977, and by members of the International Commission in November 1978, in all provinces, by age group

Age group	Survey	Number of persons examined	
		Total	With facial pockmarks[a]
Preschool children	National	271 897	0
	International Commission	3 139	0
School-age children	National	224 297	38
	International Commission	26 665	18
Adults	National	1 451 125[b]	650
	International Commission	14 307	94

[a] Due to smallpox contracted before 1972.
[b] Examined at check-points; mostly adults.

Table 26.15. Sudan: number of reported cases of and deaths from chickenpox between 1973 and 1977 and number of specimens tested

Year	Number of cases	Number of deaths	Number of specimens tested[a]
1973	5 123	0	11
1974	8 895	0	20
1975	1 832	8	11
1976	1 082	2	16
1977	758	0	16
Total	17 690	10	74

[a] None contained poxvirus.

Z. JEŽEK

Plate 26.4. The collection and testing of material from skin lesions in cases of fever with rash, especially in countries where variola minor had recently been endemic, provided assurance that the surveillance system would have detected smallpox if it had occurred.

covered evidence of possible smallpox transmission as late as November 1973. The last confirmed case in the province had occurred in November 1972, in the most densely populated part of Kapoeta District, some 80–100 kilometres from the Lafit mountains, where evidence of possible continued transmission was discovered. Intensive investigations suggested that there had been a number of cases, the last in a 15-month-old boy with facial pockmarks. However, it was impossible to determine precisely the date of onset of the disease. The surveillance team revisited the Lafit mountains 3 times in 1974, and repeatedly thereafter, but failed to find any further evidence of smallpox. During a visit to the area in 1976 evidence was obtained suggesting that the supposed last case in the focus had been infected late in 1972, not late in 1973.

Special surveillance in areas on the Ethiopian border. In September 1973, an interregional WHO smallpox eradication programme seminar was held in Addis Abeda. Border surveillance was discussed, and the Ethiopian and Sudanese governments made arrangements after the seminar for surveillance teams from each country to investigate rumours of smallpox on the other side of the border (see Chapter 21). For example, at the request of Ethiopia in November 1973 and February 1974, a Sudanese team investigated smallpox rumours and vaccinated the inhabitants in the Gabba and Metabel areas of Gojam Province in Ethiopia, which were not easily accessible from the Ethiopian side of the border.

Visit by a WHO consultant. In August–September 1977, Dr Gordon Meiklejohn, a WHO consultant, visited Khartoum and assisted in documenting the work of the smallpox eradication programme and subsequent surveillance activities. In May 1978, a further stimulus was given to the discovery of cases of smallpox by the announcement by the World Health Assembly that a reward of US$1000 would be offered to any person who reported a smallpox case which was confirmed by laboratory investigations in a WHO collaborating centre.

WHO

Plate 26.5. Some of the participants at the meeting of the International Commission for the Certification of Smallpox Eradication in the Sudan, 29 November 1978. *Left to right:* R.A. Khan (WHO), **C. Lerche (Norway), W. Koinange (Kenya), Yemane Tekeste (Ethiopia)**, A.H. El Sayed (Sudan), J.G. Breman (WHO). The names of the Commission members are in bold type.

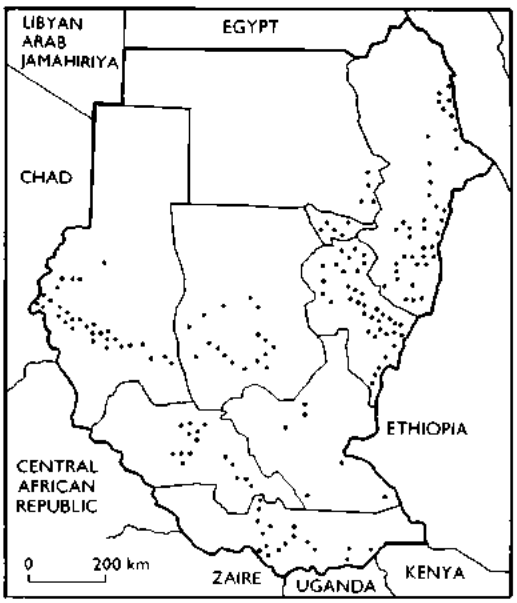


Fig. 26.8. Localities in the Sudan visited by members of the International Commission for the Certification of Smallpox Eradication, 15–29 November 1978.

Visit of the International Commission, 15–29 November 1978

After a brief meeting in Khartoum, field visits were made by 9 separate teams over a period of 12 days. Because of the large size of the Sudan, an aeroplane was made available by the United Nations Development Programme to help to cover critical areas in the northern and eastern provinces (Fig. 26.8). During their visits, Commission members carried out facial pockmark (see Table 26.14) and vaccination scar surveys.

The International Commission found nothing to cause them to doubt the claim that smallpox transmission had been interrupted in the Sudan at least 5 years earlier, and certified the country to be free of smallpox.

SOUTH-WESTERN ASIA

Several countries in south-western Asia required certification by international commissions or other special measures (Fig. 26.9). They fell into 3 groups.

Yemen and Democratic Yemen were geographically close to the last remaining endemic countries in the world, Ethiopia and Somalia, and certification activities were delayed there until nearer the time when the Horn of Africa would itself be visited by international commissions. Because of political differences between the two countries, they were visited by separate international commissions in June 1979.

To the north-east lay Saudi Arabia and the Gulf states of Bahrain, Kuwait, Oman, Qatar and the United Arab Emirates. Because of the intensity of the traffic between these countries and the Indian subcontinent and the vast annual pilgrimages to Mecca, the Consultation on the Worldwide Certification of Smallpox Eradication had recommended in October 1977 that WHO should obtain special country reports from each of them for review by the Global Commission in December 1978.

Iran, Iraq and the Syrian Arab Republic were not included in the Intensified Smallpox Eradication Programme in 1967 because they had eliminated endemic smallpox in 1963, 1959 and 1950, respectively. However, it was known that a major epidemic of variola major had spread through these countries in 1970–1972, after an importation from Afghanistan (see Chapter 23). Few of the many cases which occurred had been reported to WHO—29 from Iran in 1971 and 2 in 1972, 37 from Iraq, all in 1972, and 54 from the Syrian Arab Republic in 1972 (Fig. 26.10). Unofficial

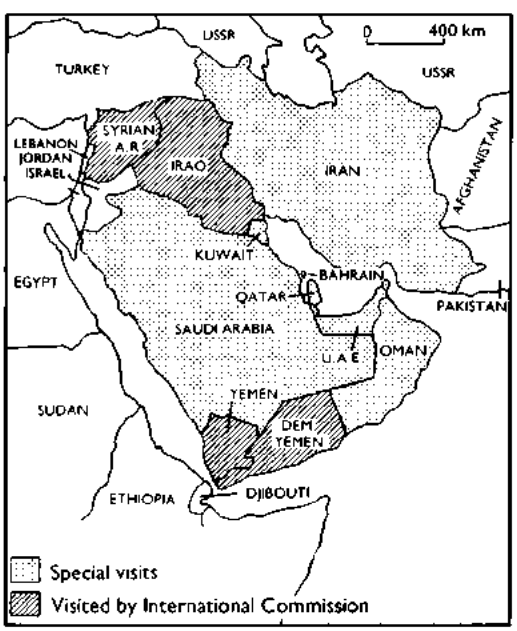


Fig. 26.9. Countries of south-western Asia and the Arabian Peninsula and the methods by which they were certified.

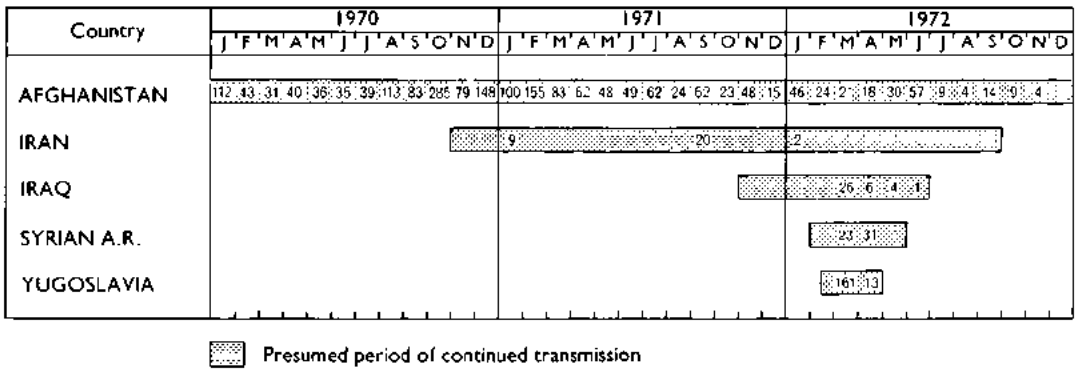

Country
1970
1971
1972
J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D
AFGHANISTAN
112 43 31 40 36 35 39 113 83 285 79 148 100 155 83 62 48 49 62 24 62 23 48 15 46 24 2 18 30 57 9 4 14 9 4
IRAN
9 20 2
IRAQ
26 6 4 1
SYRIAN A.R.
23 31
YUGOSLAVIA
161 13
Presumed period of continued transmission

Fig. 26.10. Smallpox in Afghanistan, 1970–1977, and the 1970–1972 outbreak of smallpox in Iran, following an importation from Afghanistan. The disease spread to Iraq and the Syrian Arab Republic, and from Iraq to Yugoslavia. Numbers indicate the cases officially reported to WHO by month. In both Iran and Iraq, the numbers of cases which actually occurred and were known to the respective governments were far larger (see Chapter 23).

reports suggested that there was good reason to believe that transmission had persisted for almost 2 years in Iran, 8 months in Iraq and 4 months in the Syrian Arab Republic, with many more cases than had been reported.

The last cases of smallpox in these countries were believed to have occurred in 1972, some 5 years earlier but the Consultation believed that it was important to confirm with greater certainty that smallpox was not persisting in any of them and had not been present for at least the last 2 years. It therefore recommended that visits should be made to Iran, Iraq and the Syrian Arab Republic by Global Commission members, consultants and/or WHO staff, to verify and document smallpox eradication and present their findings to the meeting of the Global Commission in December 1978.

Certification did not proceed exactly as suggested by the Consultation. Iraq and the Syrian Arab Republic were visited and certified in succession by an international commission, of which the chairman, Dr Robert Netter, was a member of the Global Commission. In Iran, however, although extensive precertification activities were conducted, political events made it impossible to arrange the planned visit of an international commission to that country.

Yemen

A WHO-assisted smallpox eradication programme had been initiated in Yemen in 1969 in the course of which the primary vaccination of 0.7 million children and the revaccination of 1 million persons, out of a population of 4.8 million, were carried out. Surveillance activities had discovered 23 possible smallpox cases between 1970 and 1977, but when specimens from these cases were examined in WHO collaborating centres no poxvirus particles were found.

In 1978 and 1979, a special search was conducted with the assistance of Mr Robert C. Steinglass, a WHO operations officer. This included the investigation of suspected cases of smallpox, the collection of specimens from every chickenpox outbreak discovered in the country, and facial pockmark and vaccination scar surveys in a large number of selected localities. Altogether 920 localities were visited in 146 of the 162 districts. The WHO reward of US$1000 for information on new smallpox cases that could be confirmed was widely publicized to stimulate the reporting of suspected cases. In contrast to African countries, in which variola minor had been most recently endemic, variola major had been the prevalent form in Yemen, and a facial pockmark survey covering some 20% of the total population revealed 1920 pockmarked persons, all of whom were over 10 years of age (Table 26.16). None of them had had smallpox more recently than 1967. None of the 42 specimens collected from cases of fever with rash was found by WHO collaborating centres to contain poxvirus.

A vaccination scar survey revealed that only 22.9% of children aged 0–4 years had vaccination scars, a proportion that rose to 65.6% among those aged 5–9 years.

Table 26.16. Yemen: results of facial pockmark survey during active searches, 1978–1979

Governorate	Villages searched		Population of villages searched	Number of persons with facial pockmarks aged:		Year of the most recent infection
	Total number	Number where persons with facial pockmarks were found		0–9 years	⩾ 10 years	
Beidha	13	12	28 376	0	36	1958
Dhamar	129	113	81 360	0	390	1964
Hajjah	110	85	72 647	0	229	1967
Harib	4	2	2 026	0	10	1953
Hodeidah	48	2	135 441	0	300	1963
Ibb	199	165	183 797	0	404	1965
Mahweet	76	50	32 266	0	93	1964
Sa'ada	52	22	27 102	0	59	1959
Sana'a	148	84	127 973	0	205	1966
Taiz	141	87	206 500	0	194	1965
Total	920	622	897 488	0	1 920	–

Visit of the International Commission, 2–10 June 1979

After preliminary discussions in Sana'a, the Commission members formed 3 teams and travelled widely throughout the country, except in the sparsely populated eastern desert area of the Marib, which was closed for political reasons. The results of the surveys confirmed those presented in the country report, and the Commission concluded that there was no evidence that there had been any endemic cases of smallpox since the last recorded cases in 1969. Accordingly, Yemen was certified to be smallpox-free.

Democratic Yemen

Although Democratic Yemen had not reported a confirmed case of smallpox since 1961, the government undertook a smallpox eradication programme, beginning in 1970. In a mass vaccination campaign combining smallpox and BCG vaccinations, 4 mobile vaccination teams had performed 1.7 million smallpox vaccinations between 1970 and 1977, among a population of 1.7 million; 578 000 were primary vaccinations, and the take rate was over 90%.

Precertification activities

Special search operations were carried out between February 1978 and February 1979, with the assistance of a WHO epidemiologist, Dr Mohamed El Naggar. The offer of a reward of 50 Yemeni dinars (approximately US$150) for the notification of a case of smallpox was publicized by newspapers, radio and television. During a year-long operation, active searches were conducted in 55 of the 83 subdistricts in the country, including 2 subdistricts on the island of Socotra. Dr R.N. Basu and Dr Holger Lundbeck, members of the Global Commission, visited the country in November 1978 to study and advise on preparations for certification.

Pockmark survey. Facial pockmarks were seen only in persons over 14 years of age (Table 26.17). From the replies to questions put to those with pockmarks, it emerged that the most recent infection among them in Democratic Yemen had occurred in 1958. A vaccination scar survey recorded 59.8% with scars in the age group 0–4 years, the corresponding proportion reaching 96.9% in the age group 5–14 years. Of 36 specimens collected from cases of fever with rash during 1978–1979 and examined by WHO collaborating centres, 8 showed herpesvirus particles and none poxvirus.

Visit by the International Commission, 3–11 June 1979

After a briefing meeting in Aden, 3 teams, each including a Commission member, a WHO consultant and a national representative, visited 18 districts and carried out limited surveys for facial pockmarks (Table 26.17) and vaccination scars. The results obtained corroborated the evidence presented in the country report.

The Commission concluded that there was no evidence that the endemic transmission or importation of smallpox had occurred in Democratic Yemen since the smallpox eradi-

Table 26.17. Democratic Yemen: results of facial pockmark surveys by national teams, February 1978–February 1979, and by members of the International Commission, June 1979, by age group

Age group (years)	Survey	Number of persons examined	
		Total	With facial pockmarks
0–4	National	23 633	0
	International Commission	922	0
5–14	National	37 921	0
	International Commission	3 431	0
⩾15	National	58 343	194[a]
	International Commission	4 572	64[a]

[a] Due to smallpox contracted before 1959.

cation programme had begun there in 1970. It certified the country to be free of smallpox.

Arab Countries of the Gulf Area: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates

The health services of these 6 countries had been greatly strengthened since the increase in income from oil production in the early 1970s. Indigenous transmission of smallpox was thought to have ceased in all of them in the 1960s, but there were numerous opportunities for importations to occur (see Chapter 23, Table 23.10) and the inadequacy of the surveillance system at that time meant that a report of zero incidence of smallpox could not be regarded as completely reliable. The 1977 Consultation on the Worldwide Certification of Smallpox Eradication had therefore requested that detailed country reports should be supplied to the Global Commission (see Chapter 24).

One of the members of the Consultation, Dr Jalal M. Aashi, who was at the time Secretary-General of the Secretariat-General of Health for the Arab Countries of the Gulf Area, arranged for a member of the Smallpox Eradication unit, Dr Ehsan Shafa, to attend the meeting of the Secretariat-General in Riyadh, Saudi Arabia, from 30 October to 2 November 1977. Dr Aashi and Dr Shafa had drawn up a plan of action for the Gulf states, to be implemented during 1978, and this was approved by the assembled ministers of health. In fact the plan was more thorough than the Consultation's suggestions had indicated. Under its terms each country was requested: (1) to carry out chickenpox surveillance and collect specimens from selected cases; (2) to establish and maintain rumour registers of suspected cases of smallpox; (3) to carry out facial pockmark surveys; and (4) to prepare a country report. Specimen collection kits and forms for each section of the plan of action were provided.

Dr Arcot G. Rangaraj, a veteran of the smallpox eradication campaign in Afghanistan, was appointed as a WHO consultant for 6 months (1 March–31 August 1978) to help to implement the plan of action. He visited each country 3 times, contacting public health laboratories, hospitals, health centres and clinics, medical officers of oil companies, missionary and other private institutions, and private practitioners.

Table 26.18. Arab countries of the Gulf area: results of precertification investigations, January–July 1978

Country	Estimated population (1977)	Facial pockmark survey in children < 10 years old		History of children with facial pockmarks	Number of cases of chickenpox reported	Laboratory investigations[a]	
		Number examined	Number with pockmarks			Number of specimens tested	Number positive for herpesvirus
Bahrain	270 000	25 623	1	Contracted in Pakistan	3 154	50	16
Kuwait	1 130 000	80 791	0	—	1 766	78	35
Oman	810 000	67 060	1	9-year-old child, skin infection in infancy	480	39	10
Qatar	190 000	15 242	0	—	566	35	8
Saudi Arabia	7 630 000	158 075	0	—	831	105	46
United Arab Emirates	670 000	85 994	4	3, each infected 7 years earlier in Bangladesh, India and Pakistan; 1, a 9-year-old boy, infected in 1971 outbreak	1 871	52	32

[a] Specimens examined at WHO collaborating centres; all were negative for poxvirus.

The results of the special investigations are shown in Table 26.18. There was no evidence that smallpox had been present in any of the 6 countries since 1971.

After reviewing the excellent data provided in the reports of these countries, the Global Commission, meeting in December 1978, had no hesitation in certifying all of them to be free of smallpox.

Iran

Preparations for certification

Shortly after the Consultation in October 1977, Dr Shafa visited Iran from 2 to 14 December 1977, during which time, in collaboration with the health authorities, a plan of operations for the confirmation of smallpox eradication was prepared. In view of the large epidemic of smallpox in Iran in 1970–1972 (see Chapter 23), government health officials agreed to carry out a comprehensive programme. This was to last for 6 months, starting on 21 March 1978 (the Iranian New Year), and include: (1) chickenpox surveillance with the compulsory reporting of cases, and epidemiological and laboratory investigation of chickenpox outbreaks associated with deaths; (2) the maintenance of a rumour register and reports on the investigation of suspected cases of smallpox; (3) facial pockmark surveys; and (4) the preparation of a comprehensive country report.

Dr Parviz Rezai, Deputy Director-General of Communicable Diseases Control and Malaria Eradication, was put in charge of the programme, and by the end of February 1978 sanitary inspectors from every province in Iran, who were responsible for specimen collection, had attended a seminar in Teheran and been issued with specimen collection kits. A seminar was also held, attended by the chiefs of the communicable disease departments of all the provinces, to discuss the plan of action and their role in its execution.

Activities went on until 23 September. Dr Shafa continued to follow their progress closely and visited Iran again in August 1978. In October, he and Dr Lawrence Brilliant, who had worked as a WHO staff member in the smallpox eradication programme in India, visited Iran to assist in the analysis of the data and the preparation of the final report for the Global Commission. They also paid brief visits to the provinces of Ilam, Fars and Isfahan. It had been planned that Dr Aashi and Henderson, members of the Global Commission, would visit Iran between 1 and 15 November, during which time they would be provided with a supplementary report giving epidemiological details of the 1970–1972 outbreak. However, their visit had to be cancelled owing to increasing civil unrest, which culminated in the deposition of the Shah and the proclamation of an Islamic Republic on 1 April 1979.

Pockmark survey. The object of the facial pockmark survey was to confirm the absence of smallpox during the previous 5 years (1973–1978); hence only children under 5 years of age were examined. The areas to be surveyed were selected in the following order of priority: (1) the environs of the last known smallpox outbreaks; (2) districts in which deaths from chickenpox had been reported; (3) districts in which suspected cases of smallpox had been reported; and (4) border territories and remote areas.

Of 72 337 children examined (1.2% of all those under the age of 5 years), 15 were reported to have apparent pockmarks. On investigation, the scarring was found to be due to chickenpox in 11 cases, to boils in 3 cases, and to the secondary infection of chickenpox vesicles in 1 case. The survey was conducted in 160 of the 162 districts, in all 23 provinces. Dr Brilliant visited the provinces of Fars and Isfahan during October 1978 and confirmed that the facial pockmark survey was well designed, the sampling frame was carefully chosen, and the survey procedures were understood by the health workers.

Chickenpox surveillance. Weekly reporting of chickenpox from each district by telegram was made compulsory for the 6-month period 21 March–23 September 1978. In all, 4076 cases were reported, giving an incidence of 12.2 per 100 000 population over a 6-month period, which was similar to incidence rates in other countries in which extensive chickenpox surveillance programmes had been undertaken. Of these reported cases, 88% were verified by senior health officials and epidemiologically analysed; 85% of the persons in question had vaccination scars. Laboratory specimens were taken from 46% of the 459 cases in unvaccinated subjects and from 140 chickenpox cases which, although the persons concerned had been vaccinated, were either severe or atypical or had occurred in an adult. Specimens were collected from every province except Boyer Ahmadi-ye Sardsir va Kohkiluyeh, Kerman, Ilam, and Lorestan.

Ilam Province, which had reported the poorest chickenpox surveillance, was visited and checked by Dr Shafa in October 1978. All 349 specimens tested by WHO collaborating centres proved negative for poxvirus.

Special investigation of suspected smallpox cases. Four unusual cases of skin disease were investigated by physicians from the Communicable Disease Unit in Teheran. Two were found to be cases of molluscum contagiosum and the other 2 were severe chickenpox. Routinely, all cases of fever with rash were regarded as suspected cases of smallpox until proved otherwise by clinical, epidemiological and laboratory findings. Between 1973 and mid-1978, 309 such cases were investigated. All proved negative for variola virus on laboratory examination by the Pasteur Institute in Teheran, an establishment which had demonstrated a good laboratory capability for smallpox diagnosis in 1971–1972.

Review by the Global Commission, 7 December 1978

Dr Rezai presented a detailed country report entitled *Smallpox Eradication in Iran*, and Dr Brilliant an additional document, *The Special Programme to Confirm Smallpox Eradication in Iran.* In addition, 2 confidential reports—*Smallpox in Iran 1970–72*, prepared by the Iranian government, and *Smallpox in Fars Province, Iran, 1970–72*, prepared by Dr Brilliant—were made available to a special group of Commission members. These 4 reports provided very comprehensive data on the smallpox situation in Iran. The confidential government report gave details of 1996 cases of smallpox that had occurred in 400 outbreaks between November 1970 and September 1972 (see Chapter 23, Fig. 23.4), of which 1349 had been confirmed as positive for variola virus in the laboratory in Teheran.

The epidemic had originated from an importation from Afghanistan and was eventually controlled by mass vaccination. Its long duration (23 months) was due to the use of poor-quality liquid vaccine, and it was rapidly controlled as soon as potent freeze-dried vaccine became available (see Chapter 23). The political decision not to report the actual number of cases to WHO did not prevent the health services from being fully operational within the country and from being committed to eliminating the disease. There was no reason to believe that any cases had occurred after September 1972.

As has been mentioned above, political circumstances had led to the cancellation of the planned visit to Iran in November 1978 by members of the Global Commission, as recommended by the October 1977 Consultation, but on the detailed evidence before it the Global Commission had no hesitation in certifying that Iran was free of smallpox.

Iraq

Smallpox had been eliminated from Iraq in 1959, so that there had been no WHO-assisted smallpox eradication programme in the country. Vaccination, and subsequently certification activities, were undertaken by the regular health services. Late in 1971, smallpox had spread from Iran to Iraq (see Fig. 26.10) but, as in Iran, the authorities had been reluctant to report it. Evidence obtained subsequently suggested that there had been at least 800 cases (see Chapter 23), but that the outbreak had been finally contained by June 1972.

Preparations for certification

In May 1978 Dr James Tulloch, a consultant with the Smallpox Eradication unit, visited Iraq to assist with the preparation of a country report and the organization of a facial pockmark survey. The basic report was prepared in collaboration with Dr Felix Jurji, the national Director of Epidemiology and Quarantine. In June, the Director-General of the Public Health Administration sent forms to all departments in the school health administration with a request that all schoolchildren should be examined for pockmarks and that the forms should be returned by mid-September for presentation to members of the International Commission, which planned to visit Iraq in October.

Visit by the International Commission, 5–15 October 1978

Because of the reluctance of the government to discuss the 1971–1972 epidemic, members of the Commission concentrated on determining whether Iraq had been free of smallpox for at least the previous 2 years. After a briefing meeting in Baghdad, Commission members and their colleagues formed 2 teams, which travelled widely through the country. They checked the quality of the

Plate 26.6. James Tulloch (b. 1949), an Australian epidemiologist who served as a consultant to the smallpox eradication programme from 1976 to 1980. He participated in the final stages of the eradication programme in Bangladesh and played an active role in preparations for certification in many countries.

reporting system, and visited hospitals, health units and the diagnostic laboratory in Baghdad. The general impression everywhere was one of competence. In the laboratory, 162 specimens collected between 1972 and 1978 from patients with a rash had been tested; all had proved negative for variola virus. Of these, 27 collected in January 1978 and 11 collected in March–June 1978 were tested in WHO collaborating centres, all with negative results.

Four out of 3825 children aged between 4 and 12 years who were examined had pockmarks, all due to smallpox contracted before or during 1972. Vaccination coverage was between 75% and 100% in primary-school children, depending on the area, and between 50% and 80% in preschool children.

The Commission concluded that there was no evidence that smallpox had occurred in Iraq since 1972 and that the health services were sufficiently reliable from the point of view of detecting, recording and reporting communicable diseases to ensure that, if a case of smallpox had occurred, it would have come to the notice of the central public health authorities. However, between their visit in October and the meeting of the Global Commission in December, the results of the facial pockmark survey had been received; these showed that 17 out of 195 665 schoolchildren had "facial pockmarks". No details were provided of the children's ages or of the dates on which they had suffered from smallpox. Certification was therefore delayed pending clarification of the situation. Subsequently, it was reported that, of these 17 children with "facial pockmarks", 16 had good primary vaccination scars, 15 cases were of chickenpox, 1 had had boils, and 1 had had another kind of skin infection. This information was sent to all Global Commission members in March 1979 and Iraq was certified to be smallpox-free by correspondence on 17 April 1979.

Syrian Arab Republic

Because endemic smallpox had been eliminated from the Syrian Arab Republic in 1950, there had never been a smallpox eradication programme in the country. All vaccinations were carried out by the regular health services. The Iran–Iraq epidemic had spread to the Syrian Arab Republic in February 1972, but appeared to have been contained by May of that year (see Chapter 23).

Preparations for certification

After his visit to Iraq, Dr Tulloch proceeded to the Syrian Arab Republic in May 1978 to help to arrange the preparation of a country report, a facial pockmark survey and the collection of specimens for laboratory testing. Dr Nouri Ramzi, Vice-Minister of Health, arranged for Dr Tulloch to visit the area of the last outbreak, in which there were 54 reported cases around Meyadin in the south-eastern part of the country, along the Euphrates river, and on the main road from Baghdad (see Chapter 23, Fig. 23.5). A survey of 507 schoolchildren in this area found 15 with facial pockmarks due to smallpox, which made it clear that more cases had occurred than were notified in 1972, as well as revealing an unreported outbreak in the period 1966–1967. For the purposes of certification it was not considered worth while to make a major effort to clarify events which had taken place over 6 years before, but the government was asked to undertake a facial pockmark survey of the 6-year-old children entering school in September. If no pockmarks were found among them, that would be considered good evidence that no cases had occurred

since 1972. Surveys carried out on 28 072 6-year-old children in 197 schools in Damascus and 11 320 children in 207 schools in Deir-ez-Zor failed to find any pockmarks. The vaccination coverage was good in schoolchildren in the higher grades—namely, 80–95%—and 50–60% among those in the first grade.

Since 1972, when 3 specimens taken from cases were found to contain variola virus by the WHO collaborating centre in Atlanta, USA, 1 specimen tested in 1974 had proved negative, as had 6 specimens tested by WHO collaborating centres between August and October 1978.

Visit by the International Commission, 15–22 October 1978

After reviewing data with the health authorities in Damascus, Commission members visited health centres and primary schools. Of 3873 children then examined, one had facial scarring reportedly due to smallpox contracted in Haffe in 1971. Four other persons with pockmarks were adults who had suffered from smallpox some 30 years previously. Commission members reviewed the reports and concluded that the detecting, recording and reporting of communicable diseases in the country were sufficiently reliable to ensure that, if an outbreak of smallpox had occurred since 1972, it would have come to the notice of the central public health authorities. Their recommendation that the Syrian Arab Republic should be certified to be free of smallpox was accepted by the Global Commission in December 1978.

SOUTH-EASTERN ASIA

At the other side of the Asian land mass were several countries in which WHO-assisted smallpox eradication programmes had never been operative because the disease had been eliminated in 1962 or earlier. The largest country, China, is the subject of detailed consideration in Chapter 27. Malaysia had eliminated endemic smallpox by the end of 1949 and effectively controlled a large outbreak that had occurred after an importation in 1959 and continued into 1960. Singapore had reported no cases since a small outbreak following an importation in 1959. Both countries had had stable governments since 1960 and the Consultation did not recommend that any special investigation should be undertaken. The remaining 4 countries were Democratic Kampuchea, the Lao People's Democratic Republic, Thailand and Viet Nam; the numbers of reported cases of smallpox in these countries during the period 1952–1963 are shown in Table 26.19.

Table 26.19. Thailand, Democratic Kampuchea, Lao People's Democratic Republic and Viet Nam: numbers of reported cases of smallpox, 1952–1963

Year	Thailand	Democratic Kampuchea	Lao People's Democratic Republic	Viet Nam
1952	43	1 740	33	2 251
1953	50	1 788	15	1 582
1954	20	443	0	3 564
1955	117	483	0	1 907
1956	4	523	0	1 008
1957	3	125	0	472
1958	28	18	0	35
1959	1 548	4	0	13
1960	32	0	0	0
1961	33	0	0	0
1962	2	0	0	1
1963	0	0	0	0

The October 1977 Consultation had recommended that, because of the prolonged hostilities and the possibility of breakdowns in the public health services, country reports should be obtained for Democratic Kampuchea, the Lao People's Democratic Republic and Viet Nam. The authorities of each of the countries concerned were to be asked to endorse these reports and, in so doing, to certify that no cases of smallpox had occurred in their country for the past 2 years. In view of the intense traffic between Thailand and India and Bangladesh, it was recommended that a member of the Global Commission or a WHO consultant should visit Thailand.

Lao People's Democratic Republic and Viet Nam

In recommending that country reports should be obtained from Democratic Kampuchea, the Lao People's Democratic Republic and Viet Nam, the Consultation had taken a cautious attitude, for there had been only 1 reported case (in Viet Nam in 1962) since 1959. Because of the fighting there during the 1960s and 1970s, large numbers of foreign soldiers had been present in these countries, but no reports of the occurrence of smallpox

had been received. Furthermore, smallpox had been absent from neighbouring countries for many years, and over the past decade there had been little communication with the endemic countries of the Indian subcontinent.

Much of the available information on Democratic Kampuchea, the Lao People's Democratic Republic and Viet Nam was in the files of the WHO Regional Office for the Western Pacific in Manila, which requested these countries in March 1978 to provide additional information. However, by August of that year no reports had been received at WHO Headquarters in Geneva. To accelerate matters, Dr Bert van Ramshorst, a medical officer in the Smallpox Eradication unit, was sent to Manila on 4 October 1978 to prepare country reports, based on the data available in the regional office, for the Global Commission meeting early in December. These were sent to the respective governments for endorsement, which was eventually received in Geneva from Viet Nam on 28 November and from the Lao People's Democratic Republic on 29 November. Thus the Lao People's Democratic Republic and Viet Nam were certified by the Global Commission on the basis of the reports prepared from the documentation available in the regional office and the official statements by their respective governments that the countries were smallpox-free. However, the certification of Democratic Kampuchea had to be deferred, because government endorsement of the country report had not been received.

Democratic Kampuchea

Formal endorsement by the government of Democratic Kampuchea of the country report prepared by the Smallpox Eradication unit proved to be very difficult to obtain because of the political turmoil in that country. Briefly, the situation was that, after a prolonged civil war, the Kampuchean National United Front for National Salvation took power in January 1979, overturning the Khmer Rouge government under Pol Pot and calling the country the People's Democratic Republic of Kampuchea. The Khmer Rouge fled, but continued to fight a guerrilla war against the new government, at the same time setting up, together with other groups, a rival coalition government. The latter was recognized by the United Nations, so that official contact with the authorities who were actually running the country, necessary in order to obtain endorsement of the country report, was not possible.

In accordance with the decision that official government endorsement of the report was essential, the Global Commission, meeting in December 1978, deferred certification. During the succeeding months WHO took a number of steps designed to break the deadlock. These included attempting to make contact with the Ambassador of Democratic Kampuchea in Beijing and approaches via Dr Robert Netter, a member of the Global Commission resident in Paris, since at that time two French groups were working in Democratic Kampuchea, as were UNICEF and the International Committee of the Red Cross.

In early autumn news came that Dr My Samody from Phnom Penh was attending a meeting at the International Committee of the Red Cross in Geneva. He was contacted and given a copy of the report. At the same time an urgent request for the endorsement of the report was addressed to the government recognized by the United Nations through its mission in Geneva, but no reply was received.

On 8 November, a letter dated 25 October 1979 was received from Dr Nu Beng, Minister of Health of the People's Democratic Republic of Kampuchea in Phnom Penh, endorsing the country report and containing a declaration of the smallpox-free status of the country. This was accepted by the Global Commission, and together with China (see Chapter 27), Democratic Kampuchea was the last country in the world to be certified, on 9 December 1979.

Thailand

In accordance with the recommendation of the October 1977 Consultation, Dr R. N. Basu, then Assistant Director-General of Health Services in India and a member of the Global Commission, visited Thailand from 8 to 27 May 1978 for an initial appraisal, field visits and the preparation of documentation. He visited Bangkok and 4 provinces, where he interviewed personnel in health offices, hospitals, clinics and schools, and also visited 2 refugee camps on the Laotian border. In the camps, he examined people for vaccination

scars, and by questioning them found that none had ever seen a case of smallpox either in the camp or in their country of origin. Dr Basu observed the way in which the communicable disease surveillance system operated in hospitals, in the 4 regional epidemiological offices, in the regional communicable disease control offices, and in remote areas, where mobile units were used for this purpose; he also evaluated the performance of the health volunteers scheme for providing primary health care at village level.

Documentation provided for the Global Commission included a comprehensive country report prepared by the government of Thailand and a paper presented by the government at the 1967 interregional seminar on smallpox eradication, which gave epidemiological details of the eradication of the disease in Thailand. The last case occurred in 1962—an importation from Calcutta, which did not give rise to any secondary cases.

On the basis of the country report and the evidence presented by Dr Basu, the Global Commission in December 1978 certified that smallpox had been eliminated from Thailand.

CONCLUSIONS

This complex series of operations, involving 29 countries in Africa and Asia over the brief period of 24 months, completed the certification of smallpox eradication in all the countries of the world in which the disease had been endemic in 1967, or countries otherwise regarded as at high risk, except for China and the countries of the Horn of Africa. Many different procedures were adopted, depending mainly on the prior history of smallpox and a variety of political considerations. There remained only the certification of China, the Horn of Africa and the adjacent country, Kenya, and the receipt from other Member States of WHO of certificates denoting freedom from smallpox for at least the preceding 2 years. These matters are discussed in the next chapter.

CHAPTER 27

THE COMPLETION OF GLOBAL CERTIFICATION: THE HORN OF AFRICA AND CHINA

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INTRODUCTION

As the eradication of smallpox was certified, country by country and region by region, global certification activities finally focused on the Horn of Africa and China (Fig. 27.1). For very different reasons, these were the last regions of the world to provide the detailed information required before the global eradication of smallpox could be certified by the Global Commission in December 1979.

The Horn of Africa comprises 3 contiguous countries, Ethiopia, Somalia, and Djibouti (Fig. 27.2), in the first 2 of which smallpox had remained endemic after it had been eliminated from every other country in the world. The eradication programme in these countries had been hindered by warfare and civil disturbances (see Chapters 21 and 22), which continued into the period of precertification surveillance and of certification itself. The last known case of endemic smallpox in the world had occurred in Merca,

Somalia, in October 1977. In Kenya, smallpox was related epidemiologically to outbreaks in Ethiopia and Somalia because of the common borders with those countries, and the 4 countries were therefore grouped together for certification purposes. Furthermore, because of the movements of nomads and refugees between them, it was essential that all 4 countries should be prepared for certification and visited by international commissions simultaneously. A symbolic target date was established for the final certification, 26 October 1979—exactly 2 years after the onset of rash in the last case in Somalia.

In China, it was believed that the last case had occurred many years earlier, but WHO had not been involved in either the eradication campaign or any follow-up activities, nor did WHO officials have access to China before 1972. Even then, it proved very difficult to obtain a satisfactory description of how and when smallpox had been eradicated until a visit by a WHO team was arranged by the Smallpox Eradication unit in July 1979. Because of the vast population and size of China, the Global Commission believed that the smallpox situation there should be properly documented before its smallpox-free status could be certified.

PREPARATIONS FOR THE CERTIFICATION OF SMALLPOX ERADICATION IN THE HORN OF AFRICA

With the global eradication of variola major in October 1975 and the imminent eradication of variola minor during 1977, there was pressure to complete certification of the global eradication of smallpox as quickly as possible, because of its implications with respect to the discontinuation of routine vaccination and the abandonment of the requirement of vaccination certificates for international travellers. Because Ethiopia and Somalia were the last countries in the world in which smallpox had been endemic, it was possible to focus all available WHO resources on this effort, and from 1977 onwards much larger international resources were directed to these countries than had ever been made available to the other countries of Africa.

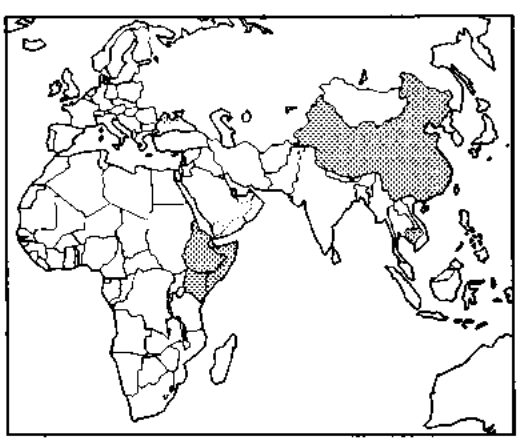


Fig. 27.1. The Horn of Africa, China and Democratic Kampuchea (see Chapter 26), the last areas in the world to be certified free of smallpox.

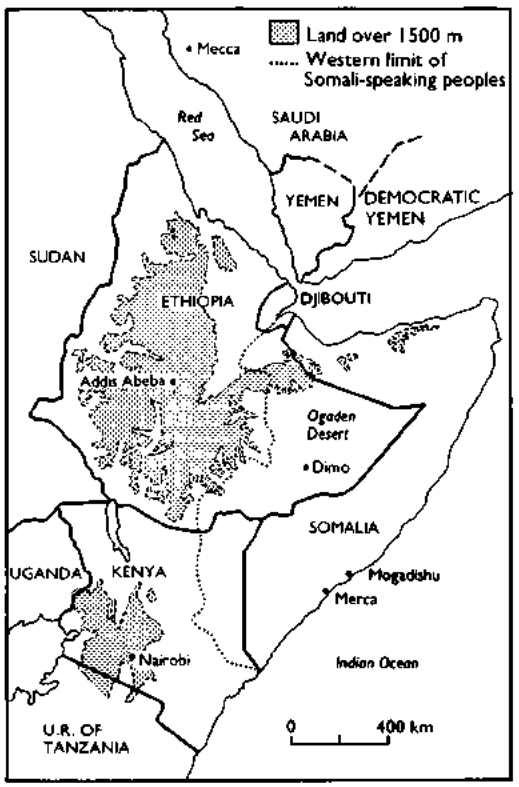


Fig. 27.2. The countries of the Horn of Africa and neighbouring parts of Africa and south-western Asia, showing land above 1500 metres. Dimo was the site of the last case of smallpox in Ethiopia, Merca that of the last case in Somalia.

The problem of certification in the Horn of Africa was further compounded by the fact that the prevalent variety of smallpox had been variola minor, and studies in the area had shown that less than 10% of patients bore persistent facial scars after recovery. Thus pockmark surveys to determine whether smallpox had recently been present were of little use, and identifying cases of chickenpox,

which might have been confused with variola minor, and obtaining specimens from them for laboratory testing, therefore became of great importance.

Coordination of Arrangements for Certification

In order to coordinate activities in the 4 countries and ensure that border areas were properly covered, the Smallpox Eradication unit organized a series of 3 coordination meetings. The first, in March 1977, was largely concerned with the completion of the eradication programme in Somalia and is described in Chapter 22; the second (September 1977) and third (April 1978) were devoted primarily to preparations for certification. Arita and Dr W. Koinange of Kenya undertook the laborious task of persuading sometimes reluctant governments to participate in these coordination activities.

Second coordination meeting, Nairobi, September 1977

In response to the emergency measures then in operation in Somalia (see Chapter 22), a second coordination meeting was held in Nairobi from 26 to 28 September 1977, 6 months after the first meeting, at a time when, as is now known, the interruption of transmission in Somalia was only a month away. It was attended by national smallpox eradication programme staff from Djibouti, Ethiopia, Kenya, Somalia, and the Sudan, together with WHO staff from the Smallpox Eradication unit and the WHO Regional Office for Africa. Despite the fact that, at the time, the Ethiopian Ogaden was occupied by the Somali army and the Western Somalia Liberation Front, a delegation from Ethiopia attended the meeting, exchanged information on surveillance activities with the participants from other countries and contributed greatly to the success of the meeting.

Discussions at the meeting were focused on how rapidly Somalia could eradicate smallpox and how the countries in the Horn of Africa could further strengthen their surveillance measures so as to prevent any further setbacks of the kind that had occurred in Somalia—namely, the establishment of new endemic foci following importations into smallpox-free areas. Important recommendations were made, among them the following:

"Smallpox surveillance activities, including specimen collection, should be increased in all priority areas of the participating countries for the next 12 months and, during this period, special attention should be paid to the possible presence of smallpox foci in both displaced populations and remote areas where search activities might have been incomplete or improperly conducted and vaccination coverage might be low.

"Special measures should be taken by all the participating countries to ensure appropriate vaccination and control of persons who travel abroad, especially those going to Saudi Arabia for the forthcoming pilgrimage. Somali medical teams going to Saudi Arabia for medical service of their pilgrims should be accompanied by experienced smallpox surveillance officers so that smallpox surveillance can be exercised during the pilgrimage period."

Third coordination meeting, Nairobi, April 1978

Since smallpox had not been reported from Somalia or elsewhere since October 1977, a third coordination meeting was held in Nairobi from 17 to 19 April 1978, specifically to discuss preparations for the certification of the Horn of Africa. It was planned that the meeting would be attended by programme staff from Democratic Yemen, Djibouti, Ethiopia, Kenya and Somalia, although at the last moment the delegates from Somalia were unable to attend owing to confusion about visas. Because of their proximity to Somalia, just across the Red Sea, it was originally intended that Yemen should also send representatives to this meeting. However, Democratic Yemen and Yemen were visited by international commissions and certified in June 1979, separately from the Horn of Africa (see Chapter 26).

The meeting decided that surveillance should continue at least until October 1979, in order to make sure that the Merca case had, in fact, been the world's last case of endemic smallpox. It was agreed that complete documentation on eradication programmes and precertification activities in the countries of the Horn of Africa should be submitted to the meeting of the Global Commission in December 1979, so as to allow it fully to appraise the progress of the programme and report its findings to the Thirty-third World Health Assembly in May 1980.

The meeting also requested WHO to offer a special reward to the first person to report an active case of smallpox anywhere in the world.

Message from the Director-General of WHO

The historical significance of the third coordination meeting in the context of the global programme was well expressed by the message of the Director-General of WHO to the meeting:

"It is now almost six months since the last case of onset of rash was recorded in the Somali smallpox eradication programme. Since that date, 26 October 1977, no further case of smallpox infection has been detected in the Horn of Africa, or anywhere in the world. This date, therefore, appears to mark the turning point in the global smallpox eradication campaign. Until then, the major objective had been to eliminate all smallpox foci. But now the situation has changed. Now it is our task to demonstrate whether we have broken the chain of smallpox transmission which has continued amongst the peoples of the world for thousands of years.

"In this respect, this meeting has a special place in the history of smallpox eradication. Proving the absence of the disease is likely to be no less difficult than containing outbreaks. There will naturally be a certain degree of doubt, since the event has never happened before in the history of medicine.

"I believe this meeting will tackle the problem of scientific credibility fully and squarely. But one point is already made clear. Surveillance, once established on a sound technical basis, should continue throughout two years following the detection of the last case. This is the only way to ensure that the international criteria of public safety have been fully met.

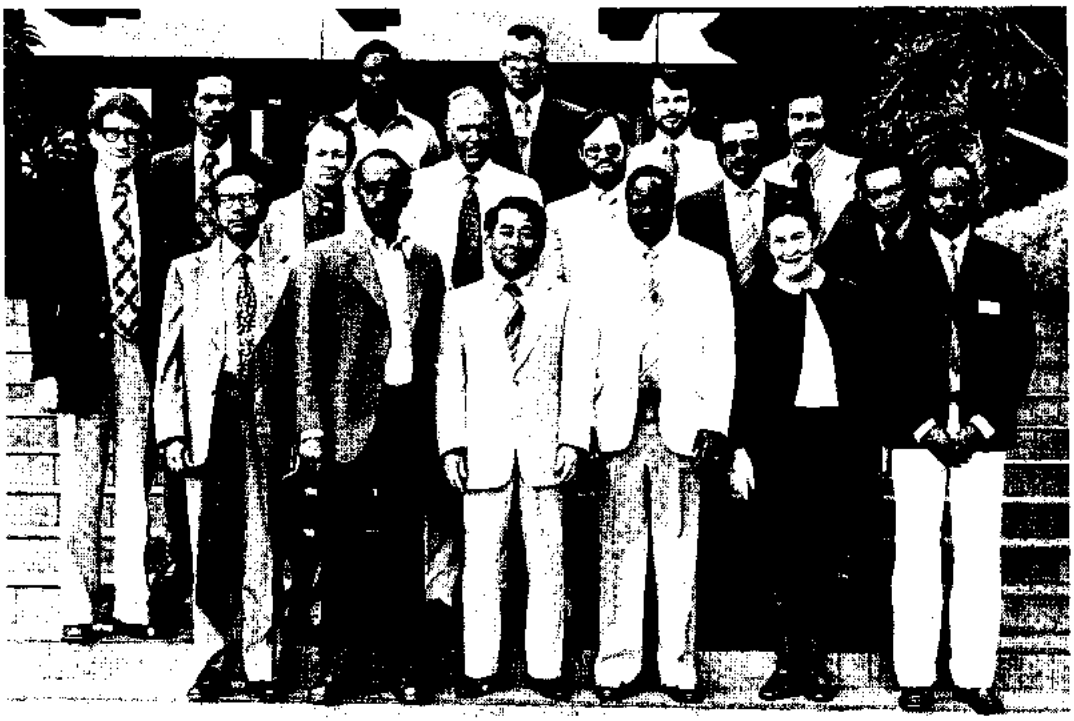
"One of the most heartening aspects of the global eradication campaign is the way the countries concerned have worked together to achieve the enormous progress made to date. Your participation in this meeting again demonstrates that sense of international solidarity, and the desire of the six countries you represent to contribute to the goal of worldwide global eradication. The most critical programmes are those in your areas. The next two years' surveillance will mark the crucial phase in the final confirmation of this worldwide achievement."

Two weeks after the Nairobi meeting, the Thirty-first World Health Assembly did establish such a reward, the amount offered being US$1000 (see Chapter 24).

Precertification activities

Intensive precertification programmes were undertaken in all 4 countries in preparation for visits by 4 separate international commissions in October 1979. The situation in each country was different. In Ethiopia and Somalia, the personnel and organization of the national eradication programmes were retained but shifted their target from the elimination of endemic foci to an active search for unreported cases. However, the ease with which these operations were accomplished differed greatly in the 2 countries. At the time, the whole of Somalia was under government control and the intensive surveillance activities developed during the eradication programme continued throughout the next 2 years. In the much larger country of Ethiopia, although active surveillance could, with some difficulty, be carried out in most of the country, the Ogaden desert, which included portions of the 3 provinces of Bale, Hararge and Sidamo, was the scene of active warfare, with armed forces moving from Somalia into Ethiopia. These disturbances greatly increased the difficulties of active surveillance. The Ogaden was clearly an area of special concern, requiring particularly intensive surveillance because, as epidemiological studies there had shown, the transmission of variola minor could be sustained for many months among comparatively small population groups (see Chapter 22).

Endemic smallpox had been eliminated from Kenya in 1969, but some importations had occurred thereafter, most recently in December 1976, in a rural area adjacent to Somalia, so that a special surveillance programme in that part of the country had had to be organized. Similarly, Djibouti had had to organize special surveillance in 1977 because of its proximity to the Ogaden, whence refugees were flowing into the country.



WHO

Plate 27.1. Participants at the third coordination meeting in Nairobi, 17 – 19 April 1978. *Left to right, front row*: Z. Islam (WHO), Yemane Tekeste (Ethiopia), I. Arita (WHO), C.L. Khamis (Kenya), B. O'Keefe (Kenya), D.W.O. Alima (Kenya); *middle row*: H.B. Lundbeck (Sweden), K.R. Dumbell (United Kingdom), S.O. Foster (WHO), V. Radke (WHO), W.M. Jaffer (Democratic Yemen), Girma Teshome (Ethiopia); *back row*: P.R. Arbani (WHO), I.P. Mwatete (Kenya), M.N. El Naggar (WHO), J.F. Wickett (WHO), R.C. Steinglass (WHO).

Precertification Activities in Ethiopia

The Ethiopian smallpox eradication programme was conducted successfully during a period of considerable political disturbance (see Chapter 21), which continued and indeed became more serious during the preparations for certification. Both the eradication campaign and the subsequent precertification operations are described in detail by Tekeste et al. (1984).

The last known case in Ethiopia occurred in August 1976 in Dimo village, El Kere *awraja*, in the Ogaden. There were then 25 WHO epidemiologists, 15 national coordinators and about 1000 Ethiopian staff in the smallpox eradication programme, using some 90 vehicles. From the end of 1976 onwards, Ato Yemane Tekeste served as the project manager of the Ethiopian smallpox eradication programme. He was assisted by 3 WHO epidemiologists (Dr Lev Khodakevich as senior adviser, Dr Claudio do Amaral and Dr Poerwokoesoemo R. Arbani) and a WHO finance officer (Mr Omar S. Ismail). Under Ato Tekeste's direction, 9 assessment officers supervised 15 programme coordinators, each responsible for one of the 15 regions, in the management, training and supervision of field staff as well as in the assessment of the programme. These coordinators employed a number of surveillance agents and intermediate supervisory staff, totalling about 1000.

With these changed staffing arrangements, the precertification activities were started early in 1977. During 1977, 1978 and 1979, when extensive searches for possible hidden foci were carried out, Eritrea as well as a number of other areas in the north and the Ogaden in the south were often partly or completely inaccessible because of civil disturbances and warfare. Accordingly, search operations were conducted or stopped as the areas became accessible or inaccessible. In border areas which became inaccessible to Ethiopian staff, rumours were investigated, wherever possible, from bases in Djibouti, northern Kenya and Somalia. This necessitated extensive coordination between the 4

countries through the exchange of reports on smallpox rumours, which was achieved by close contact between national programme directors and Arita, who frequently visited Ethiopia and the neighbouring countries.

Political events in the Ogaden

Because of military activities, precertification operations in areas under the control of the Ethiopian government were conducted differently from those in areas in which the government then had little control—namely Eritrea and the Ogaden (shown in Fig. 27.3 as a stippled area). Although the areas of limited access were geographically extensive, the majority of the population lived in the more accessible central highland areas. The last case of smallpox in Eritrea occurred late in 1972. Intensive searches in 1973–1974, before the activities of the separatist movement limited access to the rural areas, failed to reveal any evidence of further cases. The Ogaden desert, on the other hand, was the route by which smallpox had spread to Somalia in 1976 and was thus an area of great importance for surveillance.

Fig. 27.4 illustrates the changing fortunes of war in the Ogaden. Politically, the period of the smallpox epidemic in southern Somalia was marked at first by guerrilla activities in the Ogaden by the Western Somalia Liberation Front and then by the occupation of this area by the Somali army in July 1977. Eight months later the Ethiopian army recaptured the major towns, but continuing guerrilla activity prevented the resumption of normal surveillance elsewhere. By 1979 the situation had stabilized to the point where searches could be made along the western limits of the Ogaden.

Precertification activities in the accessible areas

Different parts of the politically accessible portion of Ethiopia presented somewhat different problems. Over most of the area routine surveillance was carried out through the newly established farmers' associations (see below) in the rural areas and urban dwellers' associations in the towns. In other areas special searches were organized. Certain areas were considered to be at high risk because the last cases had occurred there, access to them was difficult, or good routine surveillance had not been possible. In others, travel was safe only during a few weeks of calm between outbreaks of civil strife. Finally, there were some remote, sparsely populated areas which had been infrequently searched and which could not be reached without special logistic arrangements or transport by helicopters.

Searches in rural areas. The population of Ethiopa is predominantly rural, only 11% living in towns or villages with 2000 or more inhabitants. The search for evidence of recent smallpox in most rural areas was based on the farmers' associations, which were cooperatives comprising some 500–1000 persons. There were about 20 000 of them in Ethiopia in 1977. Because of the close contact between members of these associations and their chairmen, it was possible to acquaint them with the need for reporting smallpox cases, and during the active search operations each association became a basic unit for the collection of information on smallpox.

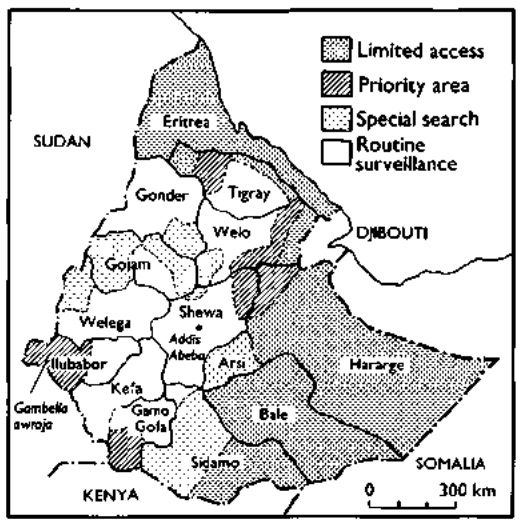


Fig. 27.3. Ethiopia: status of surveillance at the end of 1977. Throughout the programme, civil disturbances were occurring in various parts of the country so that smallpox staff were excluded from certain areas. Priority areas were defined as those difficult to reach, but where there was sometimes a calm period of a few weeks during which an intensive search could be carried out. Special searches were organized in areas which were in principle accessible, but where a satisfactory routine surveillance system could not be established. Routine surveillance was based on regular contacts with the 20 000 Farmers' Associations, whose membership accounted for two-thirds of the population of Ethiopia. For details of the search carried out in Gambella, Ilubabor, see box.

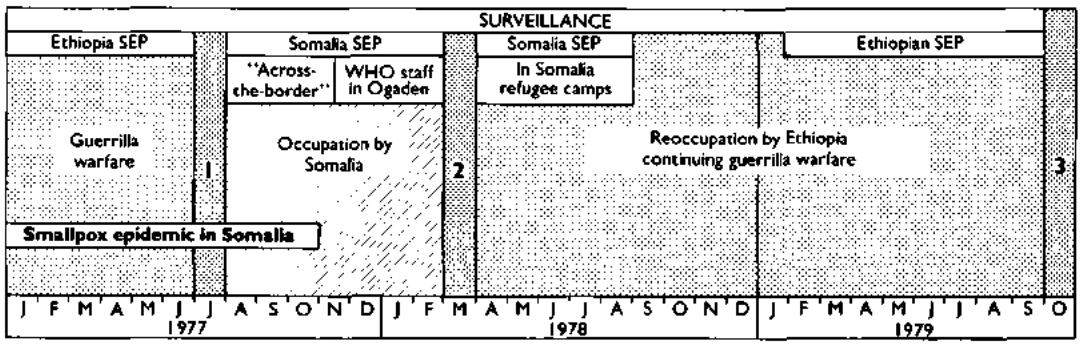


Fig. 27.4. Interplay between the changing fortunes of war in the Ogaden and smallpox surveillance activities. In July 1977 the Western Somalia Liberation Front overran the Ogaden and the Somali army established control (1). In March 1978, Ethiopian troops retook the Ogaden (2). Surveillance in varying degrees was maintained from both until eradication was certified in October 1979 (3). SEP = smallpox eradication programme.

During 1977, local surveillance teams were supposed to visit all the farmers' associations in their assigned areas 4 times a year. However, it soon became clear that coverage was erratic, 86% of the farmers' associations being visited at some time but some only once and many on several occasions. In 1978 this system was abandoned and a search for cases of smallpox was undertaken which covered some 50% of all houses in rural Ethiopia. Every month about one-fifth of all farmers' associations were visited by the surveillance workers. In this way, 20 322 out of the 20 828 farmers' associations were visited by surveillance workers between November 1978 and April 1979. The population thus contacted, either direct or through their neighbours, amounted to about 20 million—two-thirds of the total population of Ethiopia.

During the search the supervisors of the surveillance workers investigated 7260 cases of fever with rash and collected 929 specimens. A large number of cases of chickenpox and measles were seen, but no cases of smallpox.

Searches in urban areas. In addition to the searches in rural areas, the surveillance agents also searched urban areas during 1978 and 1979; thus 760 of the 929 towns, with a total population of 3.8 million, were searched, about 2500 cases of fever with rash being investigated and 189 specimens collected. Once again, no smallpox cases were found.

Second visits to the sites of the last outbreaks. During the period 1971–1976, smallpox had occurred in 99 of the 102 *awrajas* in Ethiopia. Between November 1978 and March 1979 the sites of the last outbreaks in 64 of these 99 *awrajas* were revisited by surveillance teams (Fig. 27.5). In the other 35 *awrajas*, mainly in Eritrea and the Ogaden, no such follow-up visits could be arranged because of civil strife and the resettlement of the rural population. During the visits to these 64 *awrajas*, 2 additional outbreaks were identified which had occurred before August 1976, but there were no signs of transmission after the last recorded case.

Laboratory investigations. The variety of smallpox occurring in Ethiopia in the 1970s was variola minor, which elsewhere had been found to leave facial pockmarks in less than 10% of cases. As an alternative to pockmark surveys as a way of detecting missed cases of smallpox, special attention was devoted to the surveillance of chickenpox. Large-scale collections of specimens for laboratory

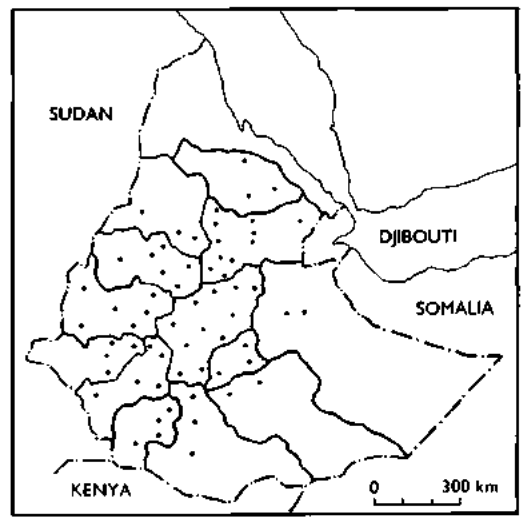


Fig. 27.5. Ethiopia: Location of the last outbreaks of smallpox in 64 accessible *awrajas* that were reinvestigated during 1979.

Search in Gambella *Awraja*, Ilubabor Region

In Ethiopia, there were a few remote and inaccessible areas in which logistically it was extremely difficult to organize a search operation, Gambella *awraja* being one of them. This remote area (see Fig. 27.3) was inhabited mainly by primitive tribal groups. No smallpox had been reported there since the start of the eradication programme in 1971, but until 1978 the only search conducted was by a team consisting of an Ethiopian surveillance agent and a United States Peace Corps volunteer, who in April–May 1972 travelled by foot for about 290 kilometres along the Gilo river towards the Sudanese border to vaccinate and search for smallpox.

In March–April 1978, a well-planned search was conducted among the 140 000 inhabitants of this area. About 60 surveillance staff worked under the supervision of 2 Ethiopian coordinators and a WHO epidemiologist, Dr Claudio do Amaral, using helicopters and river transport. About two-thirds of all the houses in the *awraja* were visited by the team; the remainder had been abandoned because the people had moved close to the river, but the team visited them by walking along the river bank. In all, 36 suspected cases were investigated and 30 specimens were collected, but no smallpox was found.

investigation were made from cases of chickenpox or fever with rash, 2886 specimens being examined between 1977 and 1979 (Table 27.1). Fig. 27.6 shows the distribution, by *awraja*, of specimens collected during 1977 and 1978.

Variola virus was not found, but herpesvirus particles were seen in about 25% of the specimens and vaccinia virus on 9 occasions. The latter resulted from contamination, since specimens were sometimes collected while vaccinations were being performed.

Table 27.1. Ethiopia: results of laboratory examinations of specimens submitted to WHO collaborating centres, 1977–1979

Year	Total number of specimens	Results		
		Variola virus	Herpesvirus	Vaccinia virus[a]
1977	676	0	161	8
1978	1 168	0	351	1
1979	1 042	0	180	0
Total	2 886	0	692	9

[a] Present as a result of contamination.

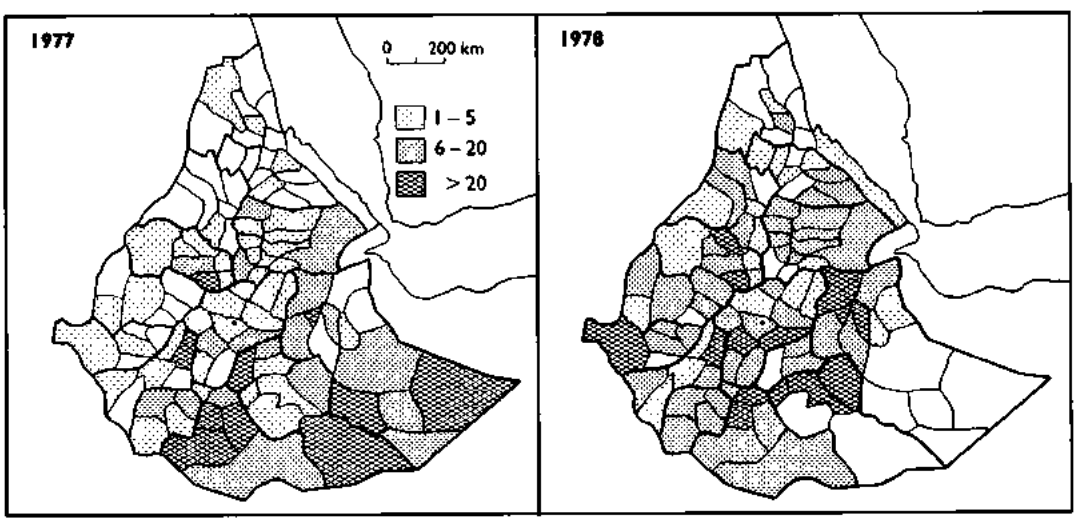


Fig. 27.6. Ethiopia: Numbers of specimens collected for laboratory examination in 1977 and 1978 by *awraja*.

Precertification activities in the Ogaden desert

The Ogaden desert, which traverses the major portion of the regions of Hararge, Bale and Sidamo (see Fig. 27.3), comprises 10 *awrajas* with a total population of about 1.4 million, most of whom are Somali-speaking nomads. It lies on a plateau bordered to the north and west by the Ethiopian highlands and to the south and east by Somalia, and by a small corner of Kenya in the extreme south-west. At its widest the desert extends 800 kilometres from east to west and 400 kilometres from north to south; it covers an area of about 200 000 square kilometres (Fig. 27.7). From the autumn of 1976 onwards the increasing guerrilla activities in the Ogaden made it more and more difficult for both WHO and Ethiopian programme staff to carry out surveillance; smallpox programme activities conducted by Ethiopian staff were finally halted in July 1977, when the Somali army invaded the area, but were resumed in March 1978, when the Ethiopian army regained possession.

Arrangements for surveillance. To cope with this situation, Arita went to Addis Abeba in mid-1977 to discuss with local WHO and Ethiopian national programme staff how best to maintain active surveillance in the Ogaden. This was of the utmost importance, because the Western Somalia Liberation Front had overrun the area, so that it was inaccessible to the Ethiopian smallpox eradication programme staff. Moreover, at that time smallpox was still endemic in southern Somalia. There was therefore a real risk that endemic smallpox might be re-established in Ethiopia, and it was essential that this should be prevented.

Two major actions were therefore taken, one in Ethiopia and one in Somalia. First, in Ethiopia a "belt" area was established between the highland areas adjacent to the

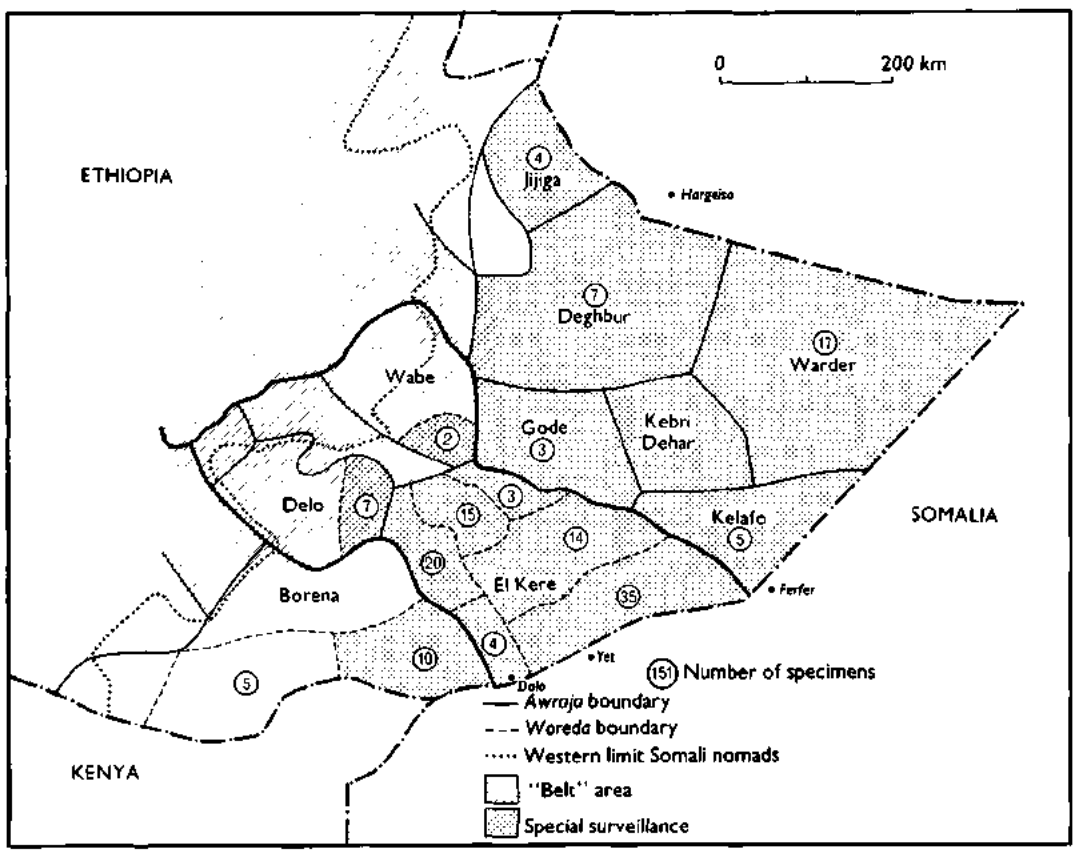


Fig. 27.7. Ethiopia: Areas of the Ogaden desert under special surveillance, showing *awrajas* in Hararge, Bale and Sidamo Regions, the western limits of the seasonal migrations of the Somali nomads, and the "belt" area where a special vaccination campaign was conducted in September-December 1977. The numbers of specimens collected for laboratory examination between July 1977 and April 1978 are shown by *awraja* and *woreda*.

Surveillance Activities and the War in the Ogaden Desert

Early in 1977, the Ethiopian national smallpox eradication programme tried to strengthen surveillance by the assignment of 4 WHO epidemiologists (Dr do Amaral, Dr Arbani, Dr El Naggar and Dr Gromyko) and national coordinators. However, because of increasing unrest in the Ogaden, their activities were limited in scope outside the capital towns of the *awrajas* of Kebri Dehar, Deghbur, Warder, Kelafo, Gode and El Kere in the Ogaden desert (Fig. 27.7).

In April, Mr William Waugh, one of the helicopter pilots working for the Ethiopian smallpox eradication programme, was kidnapped at gunpoint and held for ransom near Gode. In May, Dr do Amaral was held for 2 days in Somalia when he came too close to the border while checking a rumour in Warder *awraja*. Again in June, he was kidnapped by guerrillas in Warder *awraja* but a week later turned up in Hargeisa in northern Somalia.

In June, immediately after this incident, WHO received a cable from the United Nations Economic Commission for Africa (ECA), Addis Abeba, stating that WHO epidemiologists were taking unacceptable risks. Arita flew to Addis Abeba to attend a meeting with ECA security officials to discuss the matter. It was agreed that the withdrawal of WHO epidemiologists would in fact mean the discontinuation of precertification activities, which would be a set-back not only for the eradication campaign in the Horn of Africa, but also for the global programme as a whole. The participants agreed that minimal activities should be continued by WHO and national staff in the Ogaden, but formulated a plan for emergency evacuation, should this prove necessary.

During the last 2 weeks of July, however, the Somali army invaded and overran the entire area, forcing the withdrawal of all the WHO staff. Thus, the surveillance of smallpox by the Ethiopian smallpox eradication programme ceased in these areas until March 1978, when the Ethiopian army resumed control.

Ogaden, which were under Ethiopian control, and the Ogaden desert, stretching from Djibouti to the border with Kenya (Fig. 27.7). An intensive surveillance and vaccination programme was carried out here between September and December 1977. On average, 55% of all farmers' associations were visited each month and by the end of the 4-month campaign, virtually all had been visited by a worker from the Ethiopian smallpox eradication programme. Altogether 348 suspected cases were investigated and 272 specimens collected, but no evidence of smallpox was found.

Secondly, an attempt was made to conduct an active search from the Somali side. Efforts to achieve this by collaboration with the International Committee of the Red Cross, which was doing relief work for wounded soldiers in the Somali-occupied areas of the Ogaden, were unsuccessful, but other arrangements succeeded.

Early in September 1977, Arita organized a private meeting in Mogadishu of senior WHO and Somali staff who had extensive experience of surveillance and knew the geography of the Ogaden. It was decided to seek the agreement of the Western Somalia Liberation Front to enter the Ogaden and to employ 5 WHO epidemiologists, Dr Mohamed El Naggar, Dr Bert van Ramshorst, Dr Jean-Paul Ryst, Dr Jay S. Weisfeld and Mr Carl Hasselblad, to carry out across-the-border searches. Operational border posts were established in Hargeisa, Ferfer, Yet and Dolo (see Fig. 27.7). Many of the workers who had been employed in this area under the aegis of the Ethiopian smallpox eradication programme were recruited, because most had remained in the area after it had been occupied and were happy to return to duty. As the WHO epidemiologists could not cross the border into the area, which was under the control of the Somali army and the Western Somalia Liberation Front, experienced local workers supervised the searchers and verified rumours.

During these surveillance activities, 143 searchers visited 599 villages and 383 watering-places; 219 rumours were investigated. Posters giving information on the reward offered were displayed in each of the villages and at Koranic schools and watering-

places. The number of rumoured cases of smallpox was almost certainly exaggerated, as former Ethiopian staff had not been paid since the cessation of their programme in the area; by providing reports of possible cases of smallpox they assured their continued employment. In spite of the many suspected cases reported, experienced national epidemiologists found no evidence of continuing transmission.

In November 1977, Arita was informed by messenger that the Western Somalia Liberation Front had agreed that WHO staff could work in the Ogaden. Dr El Naggar, accompanied by a Somali counterpart, entered the Ogaden from Somalia to supervise surveillance personally and to check rumours. Because he was known to the local population, they cooperated closely with him. Borena and El Kere *awrajas* were chosen for the initial searches because they shared long borders with areas of southern Somalia in which smallpox had persisted until October 1977; furthermore, 11 of the 12 rumours of smallpox which had not been investigated by a WHO epidemiologist had originated in this area. Dr El Naggar supervised 20 searchers, who visited 33 000 houses and 300 Koranic schools. Independent assessment revealed that 94.6% of the houses had been visited by the searchers and that 51% of households knew of the reward of 200 Somali shillings (US$32). No smallpox was found.

In January 1978, Dr Rabie A. L. Khattab succeeded Dr El Naggar as the WHO epidemiologist responsible for surveillance in the Ogaden. He continued the programmes in Borena and El Kere *awrajas* and extended his activities to the adjacent *awrajas* of Delo and Wabe. With the aid of 79 searchers, 20 000 houses and 700 Koranic schools were visited, but no evidence of smallpox was found. Surveillance from the Somali side was terminated early in March 1978, when Ethiopian forces reoccupied the Ogaden, but was then resumed under Ethiopian auspices.

Laboratory investigations. During special surveillance activities in the Ogaden between July 1977 and March 1978, 151 specimens were collected from cases of chickenpox or fever with rash and tested by WHO collaborating centres. The geographical distribution of the cases from which these specimens were collected is shown in Fig. 27.7. All the important areas in which smallpox importation or transmission was suspected were covered. Half the specimens were collected in El Kere *awraja*, the area in which the last known smallpox case in Ethiopia had occurred. Four of the 151 specimens were reported to contain small numbers of pox virions, as revealed by electron microscopy. Vaccinia virus was cultured from 2 of them, while the other 2 were negative. It was found that surveillance workers were using bifurcated needles that had been used for vaccination, to dislodge scabs, so that the positive results were presumably due to contamination with vaccinia virus. The source of 1 of the 2 specimens which was negative on culture was investigated by a WHO epidemiologist, who reported that, on clinical and epidemiological grounds, the case was definitely not smallpox. It was not possible to reinvestigate the patient from whom the fourth specimen had been taken. It was collected in July 1977 in El Kere *awraja*, but intensive and continuous search between August 1977 and March 1978 failed to find any smallpox in this area.

WHO · T S SATYAN, 1975

Plate 27.2. Mohamed Noureldin El Naggar (b. 1938), Egyptian epidemiologist, joined the programme as a consultant in March 1975 in Bangladesh. After 6 months he was transferred to Ethiopia. He played a very important role in precertification activities in the Ogaden.

Precertification Activities in Somalia

When the last known case occurred in Merca, southern Somalia, in October 1977, 19 WHO epidemiologists, 27 national epidemi-

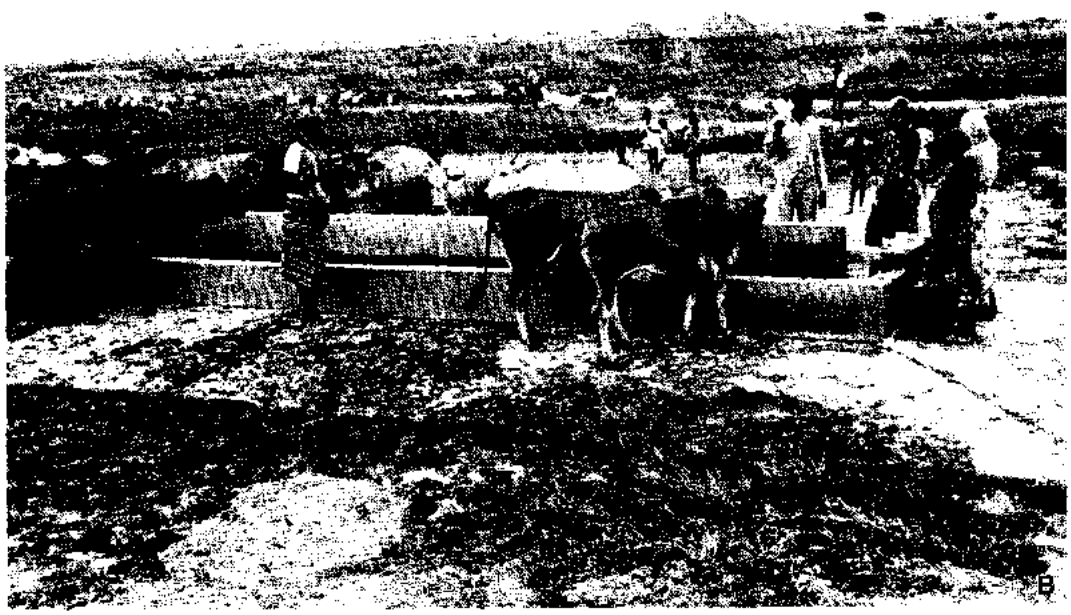


Plate 27.3. Precertification activities in Somalia. **A**: During periodic searches, a reward poster or written message was left on the door of the hut if no one was home. **B**: Watering points were natural gathering places for pastoral people and were an important source of information about nomadic groups.

ologists, and about 1600 other personnel, using 65 vehicles, were engaged in surveillance and containment measures for the smallpox eradication campaign. Dr Abdullahi Deria, director of the national campaign, and Ježek, WHO coordinator, assisted by Mr Rodney J. Hatfield, WHO administrator, directed the campaign. This impressive force continued active search operations during 1978 and 1979, as required for certification, although the number of WHO epidemiologists was reduced to 10 by the end of 1977 as activities became better organized. The eradication campaign and subsequent precertification activities have been described in detail by Ježek et al. (1981).

Development of reporting systems

Apart from one person who was infected in southern Somalia in July 1977, but moved to a military camp in the north during the incubation period, all cases in the Somali epidemic had occurred in southern Somalia. The surveillance and containment programme had therefore been focused on that part of the country. With the conversion of the programme into post-eradication active search operations, routine reporting systems were developed throughout the country. To achieve this, a smallpox office was established in each of the 16 regions and 83 districts (Fig. 27.8).

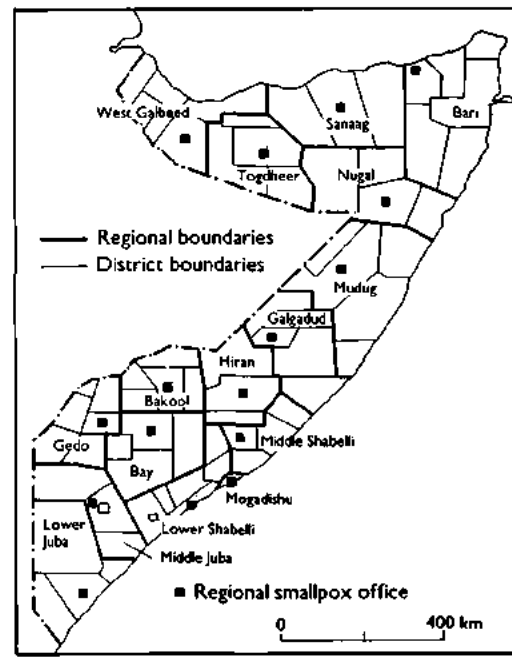


Fig. 27.8. Regions (named) and districts in Somalia. A smallpox office was established in each region and district during the period 1978 – 1979.

The regional smallpox offices were staffed by WHO or national epidemiologists and the district offices by local staff. They served to intensify the routine reporting of suspected cases of smallpox and other cases of fever with rash. A cable reporting findings was sent

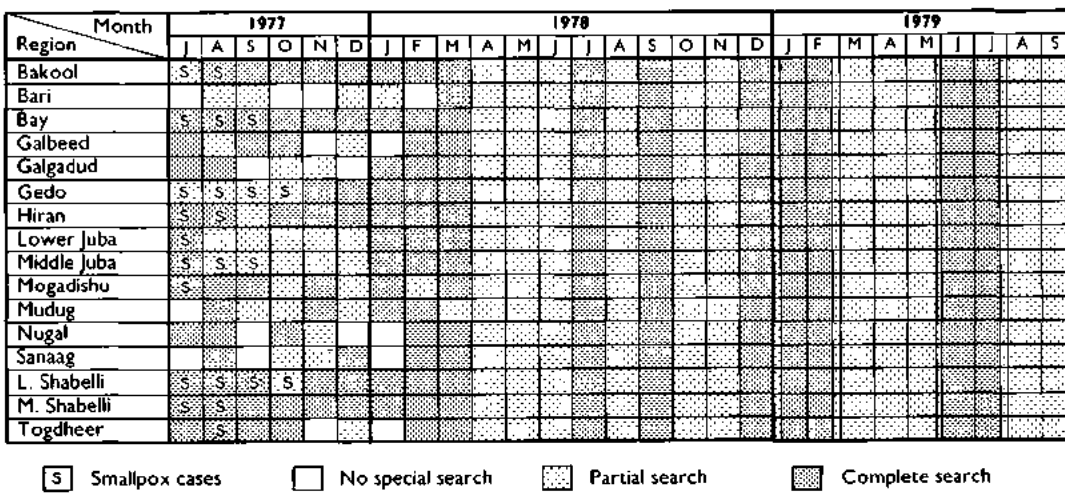


Fig. 27.9. Somalia: Frequency of search operations for cases of fever with rash, by region. Partial searches were carried out by regional surveillance teams at hospitals and markets, and in high-risk areas. Most parts of the country were searched 6 times in 1978 and twice in 1979. In 1978 the full search procedure usually lasted a month but in 1979 less frequent searches allowed greater attention to detail and more thorough independent assessment of performance.

Table 27.2. Somalia: assessment of public awareness of smallpox activities among settled and nomadic populations, July 1978–June 1979

Year	Quarter	Population type	Total number of households interviewed	Percentage who had seen:		Percentage aware of:	
				Searcher	Recognition card	Reward	Where to report
1978	Third	Settled	36 529	78	79	77	72
		Nomadic	12 776[a]	73	73	70	64
	Fourth	Settled	26 967	80	80	79	74
		Nomadic	8 810	76	69	78	68
1979	First	Settled	15 000[b]	79	79	81	74
		Nomadic	7 000[b]	67	68	68	60
	Second	Settled	17 516	78	86	81	78
		Nomadic	7 699	74	80	75	71

[a] Number of persons interviewed.
[b] Approximate figures.

every week from each district to its respective region, and from there to Mogadishu. In addition to these reports, supplementary documentation was sent to Mogadishu describing the investigation of all suspected smallpox cases or deaths associated with fever with rash.

Although new to Somalia, this reporting system proved to be most effective, almost complete returns being received from all the smallpox offices. Regional and district offices gathered comprehensive demographic data including maps showing localities, households, population, etc., which were also used for other health programmes. These had to be updated frequently as the nomadic population moved from one part of the country to another.

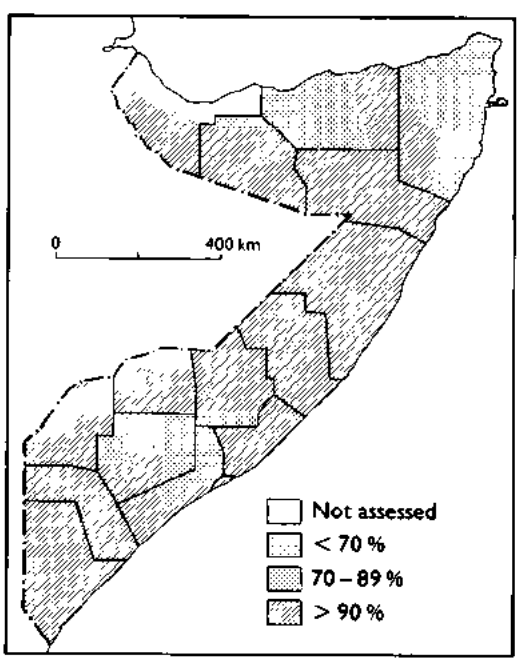


Fig. 27.10. Somalia national assessment of March 1979: percentages of localities found to have been searched in each district.

Search for cases of fever with rash

The search for cases of fever with rash which had been developed during the smallpox epidemic in 1977 (see Chapter 22) was continued throughout 1978 and 1979. Six country-wide searches were conducted in 1978 and 3 in 1979. Except in the searches carried out during the first 3 months of 1978, all districts were covered (Fig. 27.9).

Following the pattern that had been developed in India, every search was assessed by national assessment teams, which found coverage to be very good (Fig. 27.10); over 70% of the general public reported that they had seen searchers with recognition cards and knew about the reward and where to report a case of suspected smallpox if they found one (Table 27.2). The high level of awareness among the nomadic population was impressive, since these people were rarely in contact with the established health services.

Table 27.3. Somalia: results of laboratory examinations of specimens submitted to WHO collaborating centres, 1977–1979

Year	Total number of specimens	Results			
		Variola virus	Herpesvirus	Vaccinia virus	Molluscum contagiosum virus
1977	879	265	203	1	0
1978	1 646	0	463	0	1
1979	1 074	0	214	1	0
Total	3 599	265	880	2	1

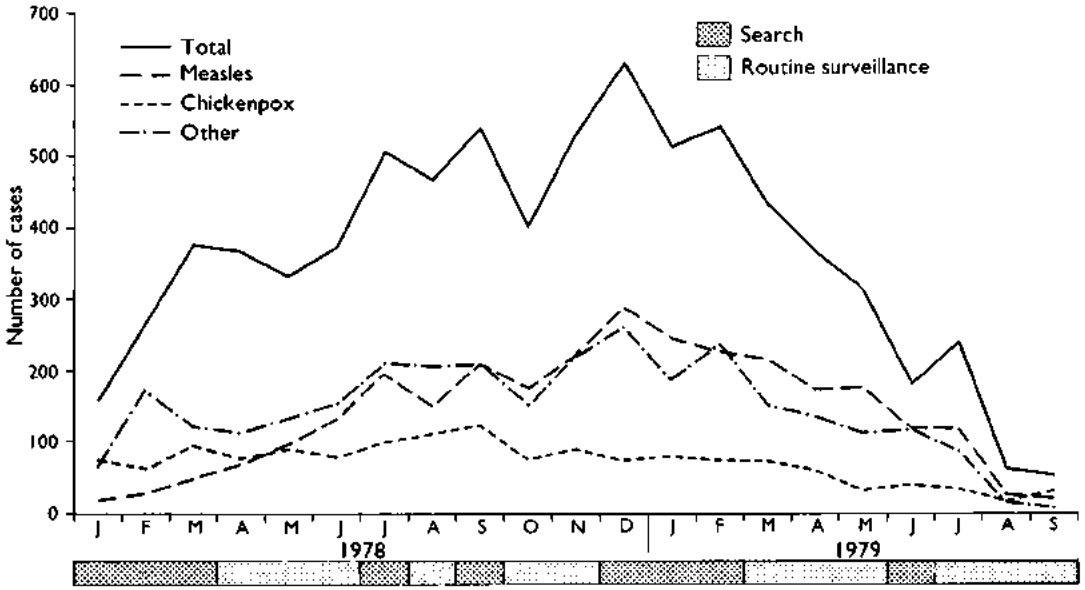


Fig. 27.11. Somalia: Number of cases of fever with rash reported monthly between January 1978 and September 1979.

In all, 19 623 cases of fever with rash were investigated in 1978 and 11 576 cases during the first 9 months of 1979 (Fig. 27.11). The diseases seen included chickenpox, measles and various other diseases associated with a rash; none proved to be smallpox.

Laboratory investigations

Laboratory specimens were collected from patients with clinically suspected smallpox and chickenpox, especially from those who had not been vaccinated, as well as from individuals affected in outbreaks of fever with rash in which a death had occurred.

Altogether 1646 specimens were collected in 1978 and 1074 in 1979, all of which were negative for variola virus (Table 27.3). Specimens were collected from all over Somalia, especially from the south (Fig. 27.12). The absence of variola virus in any of the specimens gave staff confidence that variola minor had not been misdiagnosed as chickenpox.

Precertification Activities in Kenya

Despite strenuous efforts, Kenyan and WHO epidemiologists had not been able to identify the geographical source of the outbreak of smallpox in Mandera District, northern Kenya, which occurred between December 1976 and February 1977, but it was thought to have been the result of importation from Somalia (see Chapter 19). During 1978 and 1979, searches in Kenya were conducted by staff recruited within the districts to be searched, and supervised by local health workers and senior health officers from the Division of Disease Control of the Ministry of Health, Nairobi. Dr W. Koinange, a Kenyan member of the Global Commission, Dr Ziaul Islam and Mr Vincent Radke contributed to the development of the Kenyan certification work. The Ministry of Health offered a reward of 200 Kenya shillings (US$25) for any confirmed smallpox case, and the radio and press publicized the search operations and the need to report promptly any cases of fever with rash to the staff of the nearest health unit or to other government officials.

Special searches

High-risk areas were designated, essentially those bordering on Ethiopia and Somalia (Fig. 27.13), and special searches conducted in them. Searches were supervised at three levels: (1) by the public health technician (daily supervision); (2) by senior supervisors from the district headquarters; and (3) by independent assessment teams consisting of both national staff and their WHO counterparts working in the Division of Disease Control.

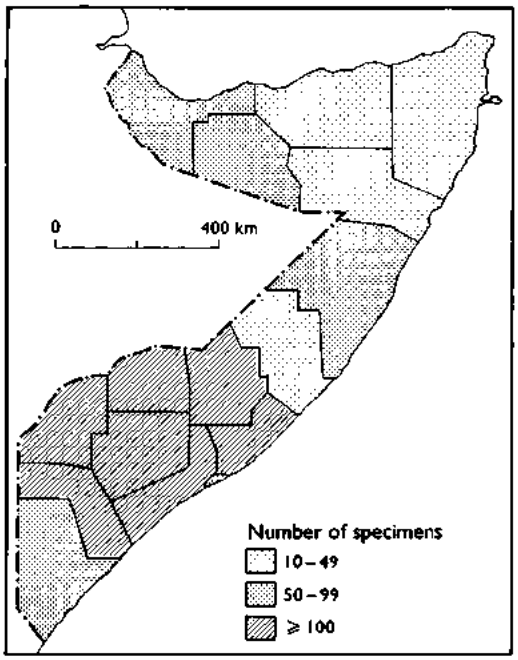


Fig. 27.12. Somalia: Number of specimens collected for laboratory examination from cases of fever with rash during 1978, by region.

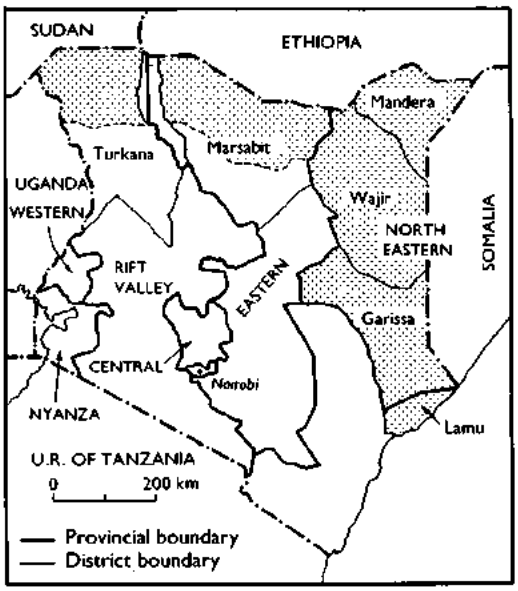


Fig. 27.13. Kenya: Areas of high priority for active search operations in 6 northern districts.

The searches in the high-risk districts of Mandera, Wajir, Garissa and Marsabit were conducted between September 1977 and March 1978, 189 searchers and 43 supervisors, with 16 vehicles, being employed (Table 27.4). They covered over 440 000 persons in an area of 200 000 square kilometres.

In Mandera District, 6 searches were conducted, although occasionally some areas were not accessible to the local searchers and supervisory staff because of bad weather or for security reasons. Out of 134 rumours received only 2 could not be checked immediately because of security problems, but were checked later when the areas were visited.

In Wajir District, areas bordering on Ethiopia and Somalia were given priority in surveillance and vaccination activities. At the time, a large number of people had crossed from Ethiopia into northern Kenya to escape the conflict in the Ogaden and in search of water and grazing land. As rumours of smallpox from the Ethiopian side of the

Table 27.4. Kenya: results of active search operations, September 1977–March 1978, by district

	District				Total
	Mandera	Wajir	Garissa	Marsabit	
Number of searchers	86	35	36	32	189
Numbers visited and revisited:					
Localities	797	943	607	106	2 453
Houses	59 700	36 133	16 605	12 228	124 666
Persons	200 931	150 265	59 039	30 436	440 671
Tea-shops	55	24	143	16	238
Watering-places	97	101	157	37	392
Schools	23	39	52	14	128
Markets	24	27	25	6	82
Ration distribution points	13	8	14	0	35
Numbers of:					
Rumours received	134	35	19	54	242
Rumours investigated	134	32	19	54	239
Cases of smallpox	0	0	0	0	0
Cases of chickenpox	57	25	5	16	103
Cases of other diseases	75	7	14	38	134
Specimens collected	57	25	5	16	103

WHO/A SAA & H. NASIF

Plate 27.4. Pilgrims' tents near Mecca in Saudi Arabia. The annual influx of people from the Muslim world provided an explosive potential for the spread of smallpox.

border came to the attention of Kenyan teams, they crossed the border to investigate whenever the security situation permitted. Five searches were conducted in the district and 35 rumours of possible cases were recorded. Only 3 rumours, all from the Ethiopian side of the border, could not be investigated because of security problems. However, cross-notifications were made to the Ethiopian health authorities through WHO in Geneva. Although Garissa District was not as important epidemiologically as Mandera and Wajir Districts, 4 searches were conducted there and 1 search in the northern area of Marsabit District.

A cluster sampling technique was used in assessing the search operations, 118 out of 120 localities sampled being assessed (98.3%) and 905 people interviewed. Of the latter, 72% reported that they had seen the searchers, and 75% had a smallpox vaccination scar.

Laboratory investigations

In 1978 and 1979, 1599 specimens were collected in high-risk areas and tested by WHO collaborating centres, with negative results.

Precertification Activities in Djibouti

Whenever famine or political unrest occurred in the Ogaden desert, many refugees fled to Djibouti. Between June and December 1977, when Somali troops invaded the Ethiopian Ogaden, some 10 000–20 000 refugees crossed into Djibouti, camping mainly in Djibouti City, Dikhil and Tadjoura.

On his return from the second Nairobi coordination meeting in September 1977, the representative of Djibouti, Dr A. A. Warsama, began work aimed at strengthening the local vaccination programme as well as surveillance for the detection of imported cases of smallpox. In November–December 1977, Dr Nicole Grasset visited Djibouti to work with the programme in conducting a special search for smallpox among the refugees. Dr Jean-Paul Ryst assisted the programme from September 1978 to October 1979 and Dr Arnaud Trébucq between May and December 1979.

The 1977 vaccination campaign reached 94 289 persons in Djibouti City, out of an estimated total population of 150 000. In December 1977, a vaccination scar survey of

1517 persons found 90% or more with scars in each age group.

Active search operations

Active search operations were planned in November 1977. The smallpox eradication programme activities were widely publicized, in particular the reward of 5000 Djibouti francs (US$28) which would be given to anyone reporting a case of smallpox. An appeal from the President of the Republic to the population to collaborate actively with the programme and announcing the reward was published in the local press and read over the radio in Afar, Somali, Arabic and French. Any cases of fever with rash found during the search were to be reported to the supervisor or the Chief of the Department of Hygiene and Epidemiology on the same day. Refugees were vaccinated if they did not have a vaccination scar.

Full coverage of this small country was achieved in the course of 2 search operations, the first between December 1977 and January 1978 and the second between February and April 1978. In the second search, 20 chickenpox cases were found but no case of smallpox. Altogether 142 specimens were collected during 1978 and 1979 and tested by WHO collaborating centres; none contained variola virus.

Smallpox Surveillance among Muslim Pilgrims from the Horn of Africa

The pilgrimage season, during which over a million Muslims from about 40 countries visit the holy towns of Mecca and Medina, occurs in November–December. Even before the season starts, the number of international travellers to Saudi Arabia increases.

In 1977, the Saudi Arabian health authorities set up smallpox surveillance centres in Jeddah, Medina, Mecca, Mona and Arafat. A circular was sent to all medical groups concerned with the health problems of the pilgrims, indicating that any suspected case of smallpox should be promptly reported and investigated.

The Saudi Arabian health service checked all pilgrims on their arrival at ports of entry to ascertain whether they had an appropriate certificate of smallpox vaccination. Pilgrims from Djibouti, Ethiopia, Kenya and Somalia were examined to see whether they had vaccination scars. Pilgrims from Ethiopia and Somalia also had to submit particulars of their itinerary, intended address, the name of their guide, the name of the regions from which they came and whether they knew of any smallpox cases in their villages during the previous 3 months. Somali pilgrims were all vaccinated on arrival, regardless of their vaccination history, and the Somali govern-

WHO

Plate 27.5. Members of the preliminary international commission that visited Ethiopia in April 1979 listening to the report being made by their chairman (Dr J. Kostrzewski) and rapporteur (Dr K.R. Dumbell) to Wogayehu Sahlu, permanent secretary of the Ministry of Health, Ethiopia. *Left to right, front row:* Taddesse Alemu (Ethiopia), Fekade Tsegaye (Ethiopia), L.N. Khodakevich (WHO), Wogayehu Sahlu (Ethiopia), T. Olakowski (WHO); *middle Row:* N.A. Ward (United Kingdom), R.N. Basu (India), Z.M. Dlamini (Swaziland), H.B. Lundbeck (Sweden), C. do Amaral (WHO); *back row:* O.S. Ismail (WHO), Haile Miriam Kahssay (Ethiopia), A.I. Gromyko (WHO), Unidentified participant, Assefa Gobeze (Ethiopia).

ment sent smallpox surveillance teams to accompany the Somali pilgrims during their trip, to deal promptly with an outbreak should it occur. Foreign medical missions collaborated fully in these surveillance activities, making regular inquiries about cases of fever with rash. Saudi Arabian medical officers at Jeddah, Mecca and Medina visited Ethiopian and Somali camps at least twice a week. No case of smallpox was found. A total of 22 specimens collected from patients suffering from fever with rash were all negative. These activities were supervised by Dr Ehsan Shafa from the Smallpox Eradication unit, who worked in Saudi Arabia between 3 November and 9 December 1977.

CERTIFICATION OF SMALLPOX ERADICATION IN THE HORN OF AFRICA

Since endemic smallpox had persisted in the Horn of Africa for many months after it had been eradicated from all other parts of the world, the certification of smallpox eradication in the countries concerned had important implications in terms of vaccination requirements throughout the world. The Smallpox Eradication unit therefore went to considerable trouble to organize certification activities and, believing that the last endemic countries could be certified by the commissions, prepared to publicize the event. Arrangements were made for all 4 countries to be visited simultaneously in October 1979 by separate international commissions, which would then meet in Nairobi to discuss their respective findings and announce the certification of smallpox eradication for the Horn of Africa as a whole on 26 October 1979, exactly 2 years after the recognition in Somalia of the world's last case of endemic smallpox. Arrangements were made in advance with representatives of the world media in order to ensure public recognition of the global eradication of smallpox.

By September 1979 each of the 4 countries concerned had prepared a comprehensive report on its national eradication programme and precertification activities. These reports were submitted in advance to the members of the respective international commissions before their visits. In order to coordinate arrangements, the chairmen of the 4 international commissions met at WHO Headquarters in Geneva and discussed the strategy of their activities in each country and at the combined meeting in Nairobi. Prior to this, however, preliminary visits were made to Ethiopia.

Preliminary Visits to Ethiopia

Two preliminary visits to Ethiopia by some Commission members were arranged, from 31 May to 15 June 1978 and from 3 to 18 April 1979, because Ethiopian certification involved some areas that were not fully under government control, and many high-priority areas were situated in regions in which travel was extremely difficult. The first visit, by Dr Keith Dumbell and Dr P. N. Shrestha, led to a joint decision by the Ethiopian government and WHO to carry out a single thorough search, instead of a multiplicity of searches, which were always incomplete and in fact beyond the capacity of the programme staff available.

In the second visit in April 1979, 7 commission members, of whom only Dr Jan Kostrzewski (chairman) and Dr Dumbell (rapporteur) also served on the final Ethiopian International Commission in October (see Chapter 24, Annex 24.1), went to Ethiopia. The group visited all the regions and 70 of the 102 *awrajas*, mainly in the highland areas, so that in October 1979 the final visit by

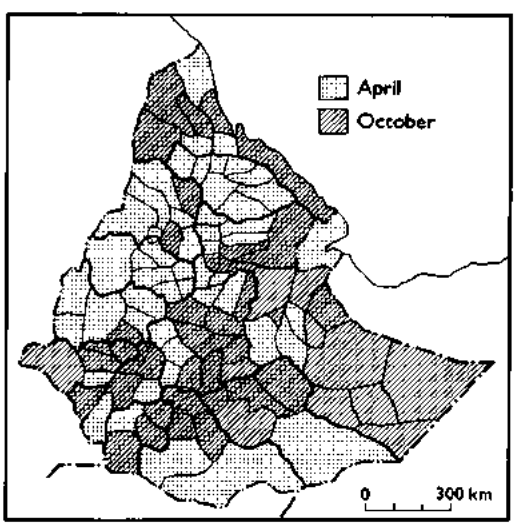


Fig. 27.14. Ethiopia: *Awrajas* visited by the members of the International Commission for the Certification of Smallpox Eradication in Ethiopia on a preliminary visit 5–16 April, on the final visit by the Commission 4–14 October 1979, and on both occasions.

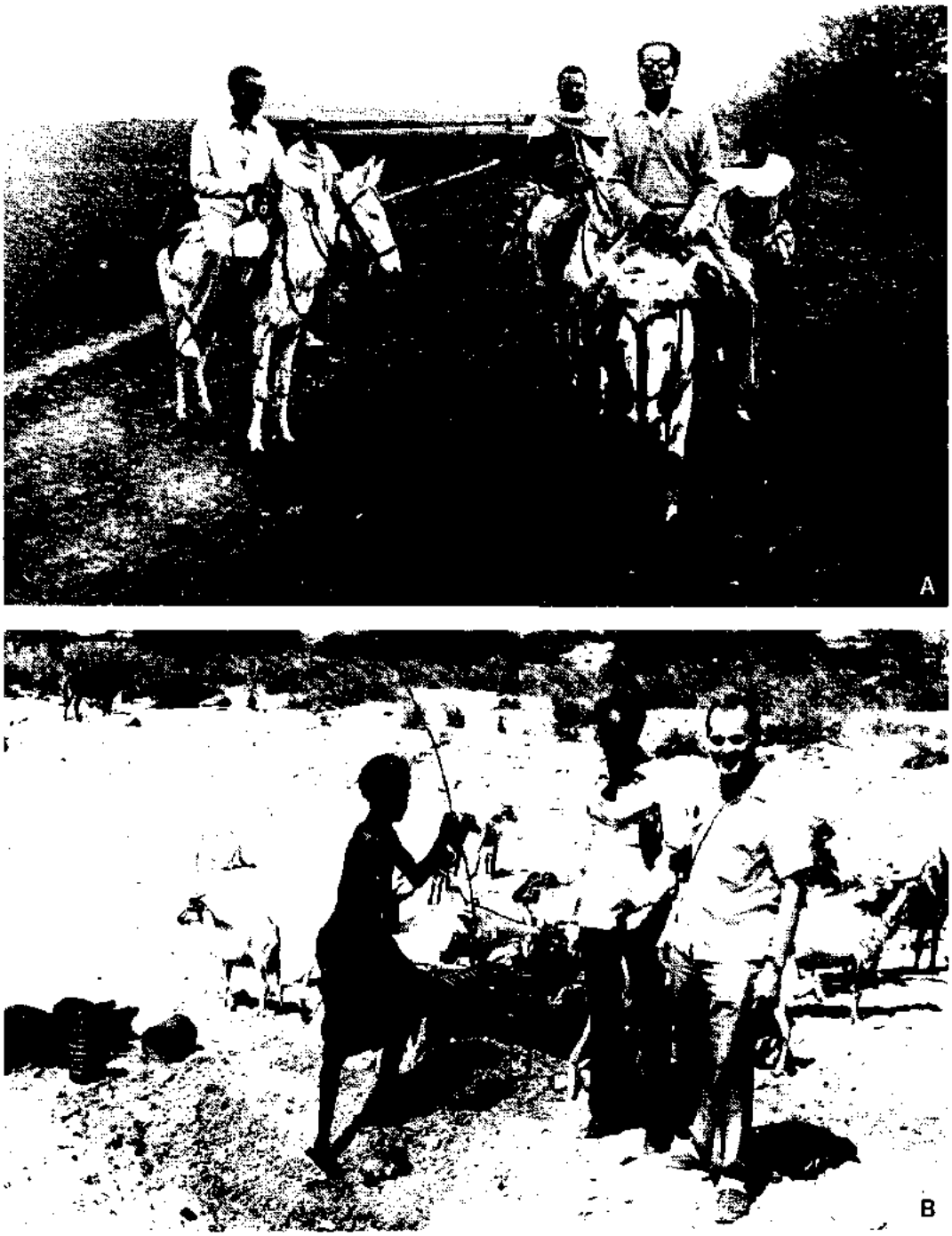
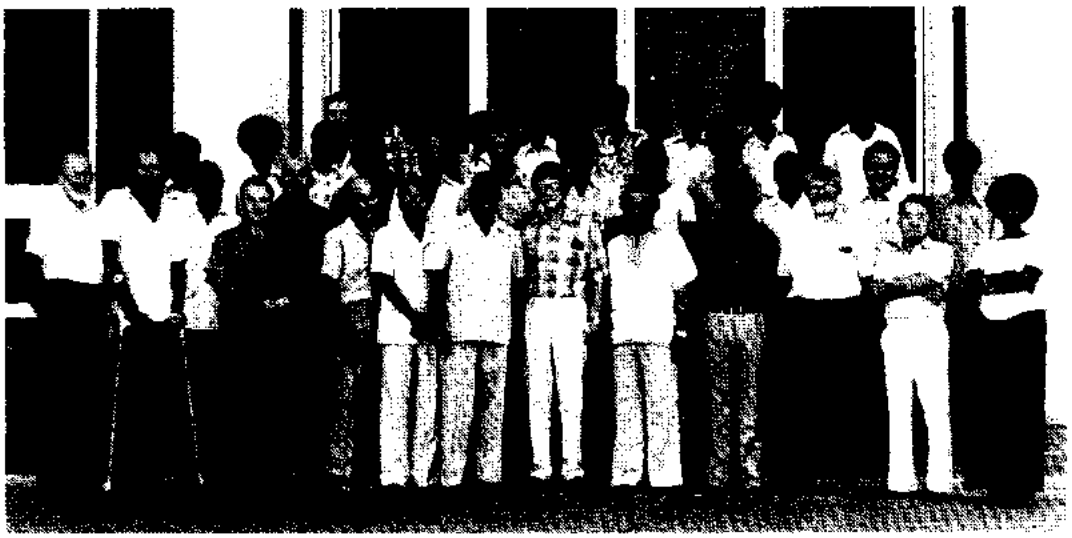


Plate 27.6. Field visits by members of international commissions. **A**: R.N. Basu, a member of the preliminary international commission which visited Ethiopia in April 1979, riding by mule between villages in a remote part of the country. **B**: R. Netter, chairman of the international commission in Djibouti, on a field visit.



WHO

Plate 27.7. International Commission for the Certification of Smallpox Eradication in Somalia with programme staff, October 1979. *Left to right, front row:* V. Zikmund (WHO), B. Kříž (WHO), A. Deria (Somalia), Z. Ježek (WHO), F. Partow (WHO), **T.J. Geffen (United Kingdom), P.N. Shrestha (Nepal)**, M. Rabile Good (Somalia), **H.B. Lundbeck (Sweden), J.M. Aashi (Saudi Arabia), Z.M. Dlamini (Swaziland), J.D. Millar (USA)**, I. Arita (WHO), Z. Ali Henry (Somalia); *middle row:* A.L. Khattab (WHO), D. Shire (Somalia), M.A. Gure (Somalia), M.T.A. Gaafar (Egypt), M.N. El Naggar (WHO), M.Adan Abdulle (Somalia), I.O. Awad (Somalia), A. A. Beira (Somalia), M.S. Mohamed (Somalia), W. Hardjotanojo (WHO), M.A. Jama (Somalia); *back row:* R.J. Hatfield (WHO), A.A. Farah (Somalia), A.S. Hassan (Somalia), A.M. Ahmed (Somalia), M. Yusuf (Somalia), H. Alaso (Somalia), J.M. Jussuf (Somalia). The names of the Commission members are in bold type.

the International Commission would be able to concentrate on critical areas in the Ogaden (Fig. 27.14).

Visits by the International Commissions

Separate international commissions visited the individual countries of the Horn of Africa during the first 3 weeks of October 1979, as follows:

	Date	*Commission chairman*
Djibouti	9–18 October 1979	Dr R. Netter
Ethiopia	1–17 October 1979	Dr J. Kostrzewski
Kenya	1–19 October 1979	Dr R. N. Basu
Somalia	1–21 October 1979	Dr H. Lundbeck

The 20 members of the 4 international commissions travelled extensively in their respective countries. In Ethiopia, because of the difficult terrain, a fixed-wing aircraft and helicopters were placed at the disposal of commission members, who used them to travel extensively throughout the country and to visit areas not accessible by overland travel. Since variola minor had been prevalent in these areas, the commissions paid special attention to the laboratory investigation of 6671 specimens collected from cases of fever with rash in the 4 countries during 1978 and 1979; all proved to be negative for smallpox (Table 27.5).

In each country, the commission members were satisfied with the data presented on past surveillance activities and certified that the country concerned had been free of smallpox for at least the previous 2 years.

Joint Meeting in Nairobi

After the certification of the individual countries had been completed, all members of the 4 international commissions and a number of others involved in the smallpox eradication programme, including 12 members of the Global Commission, some of whom had not been members of the international commissions, met in Nairobi, where the chairmen of the 4 commissions presented their respective reports. Having agreed that endemic smallpox no longer occurred in the Horn of Africa, and taking into consideration the recommendations presented in the reports of the 4 commissions, the joint meeting made the following recommendations:

(1) Smallpox vaccination should be terminated throughout Djibouti, Ethiopia, Kenya and Somalia.

(2) Vaccination certificates for smallpox should no longer be required of any travellers coming to, or leaving, the 4 countries.

(3) Experience from previously certified countries indicated that smallpox rumours would continue to occur even after certification. All such rumours were to be reported promptly to national authorities and thoroughly investigated by competent personnel, and the findings transmitted to WHO, so as to minimize unnecessary national and international concern. Specimens should be collected if necessary and sent through WHO, Geneva, to the WHO collaborating centres.

On 26 October 1979 a conference organized by the Smallpox Eradication unit was held in the Kenyatta Hall, Nairobi, in the presence of the Director-General of WHO, Dr Halfdan Mahler, the Regional Director for Africa, Dr Comlan A. A. Quenum, and the Regional Director for the Eastern Mediterranean, Dr Abdul H. Taba. Dr Kostrzewski, as the chairman of the joint meeting of the individual commissions, reported to Dr Mahler the commissions' conclusion that smallpox had been eradicated in the Horn of Africa. Immediately after this meeting, Dr Mahler sent the following message by cable or telex to all Member States and to international organizations:

"The Director-General of the World Health Organization presents his compliments and has the honour to ... inform you that International Commission today certified smallpox eradication in Horn of Africa which was last stronghold of disease Stop I personally believe smallpox has now been eradicated throughout world and am confident that Global Commission for Certification of Smallpox Eradication will confirm this in December 1979 Stop I shall then present final report to World Health Assembly in May 1980 Stop World Health Organization has accomplished this mission with support and participation of all Member States"

On the same date, 26 October 1979, in the *Weekly epidemiological record*, health officials throughout the world were informed of the successful certification of smallpox eradication in the Horn of Africa (Plate 27.8).

The certification of the Horn of Africa meant that all countries in Africa had been certified. However, neither the Global Commission nor WHO was yet able to make a definitive statement on global eradication, since smallpox eradication in China had not yet been certified.

Table 27.5. Horn of Africa: numbers of specimens tested by WHO collaborating centres during 1978 and 1979[a]

Country	Population, 1979[b] (millions)	Year	
		1978	1979
Djibouti	0.3	67	75
Ethiopia	31.4	1 168	1 042
Kenya	16.1	126	1 473
Somalia	4.3	1 646	1 074
Total	48.9	3 007	3 664

[a] All were negative for variola virus.
[b] Population data from United Nations (1985).

CERTIFICATION OF SMALLPOX ERADICATION IN CHINA

After the Second World War, civil war broke out in the Republic of China. In October 1949, after the defeat of the Kuomintang government, the government of the People's Republic of China was established and controlled the whole of mainland China. However, the Kuomintang government, which controlled only Taiwan, was until 1971 recognized by the United Nations as having the right to represent the entire country. Obviously, the Kuomintang government was unable to provide WHO with data about smallpox on the mainland. WHO was therefore not in a position to receive information on mainland China until 1972, when it followed the policy of the United Nations and recognized the government of the People's Republic of China as the only government having the right to represent China.

Lack of Information on Smallpox Eradication

Although mainland China was in theory accessible to WHO representatives from 1972 onwards, for several years it was very difficult to obtain information on health matters. From the outset of the global eradication programme, the Organization was understandably concerned about the smallpox situation in the most populous country in the world. Discussions in Geneva with Dr Chang

Wkly Epidem. Rec. / Relevé épidém. hebd. : 1979, 54, 329-336

No. 43

WORLD HEALTH ORGANIZATION
GENEVA

ORGANISATION MONDIALE DE LA SANTÉ
GENÈVE

WEEKLY EPIDEMIOLOGICAL RECORD
RELEVÉ ÉPIDÉMIOLOGIQUE HEBDOMADAIRE

Epidemiological Surveillance of Communicable Diseases
Telegraphic Address: EPIDNATIONS GENEVA *Telex 27821*

Service de la Surveillance épidémiologique des Maladies transmissibles
Adresse télégraphique: EPIDNATIONS GENÈVE *Telex 27821*

Automatic Telex Reply Service
Telex 28150 Geneva with ZCZC and ENGL for a reply in English

Service automatique de réponse
Télex 28150 Genève suivi de ZCZC et FRAN pour une réponse en français

26 OCTOBER 1979 — 54th YEAR — 54e ANNÉE — 26 OCTOBRE 1979

NO SMALLPOX
26 October 1977
to
26 October 1979

2
YEARS / ANS

SANS VARIOLE
26 octobre 1977
au
26 octobre 1979

Exactly two years to the day have elapsed since this man fell ill with smallpox in the town of Merca in southern Somalia. He is the world's last known case of endemic smallpox.

The basic criterion for confirming the eradication of smallpox is that two years must have elapsed without a case of smallpox being detected by a system of surveillance sufficiently sensitive to have detected a case had it occurred.[1] This criterion has now been met. The evidence will be subjected to critical review by a panel of experts, the Global Commission for the Certification of Smallpox Eradication. Their report will be the basis of a presentation to the World Health Assembly in May 1980. The endorsement of eradication will signify formal recognition that routine smallpox vaccination and vaccination certificates are unnecessary. The risk of complications from vaccination is obviously greater than the risk of getting smallpox which is now zero.

[1] Wld Hlth Org. Techn. Rep. Ser., 1972, No. 493.

Deux années exactement se sont écoulées depuis que cet homme a contracté la variole dans la ville de Merca en Somalie du Sud. Il s'agissait du dernier cas connu au monde de variole endémique.

Le critère fondamental de confirmation d'éradication de la variole est que deux années se soient écoulées sans qu'un cas de variole ait été décelé par un système de surveillance suffisamment sensible pour avoir pu détecter tout cas qui se serait produit.[1] Cette condition se trouve maintenant remplie. Les pièces du dossier feront l'objet d'un bilan critique de la part d'un groupe d'experts, à savoir la Commission mondiale pour la Certification de l'Eradication de la Variole. Le rapport de cette Commission servira de base à un exposé qui sera présenté à l'Assemblée mondiale de la Santé en mai 1980. L'entérinement de l'état d'éradication apportera la confirmation officielle que la vaccination antivariolique systématique et l'exigence de la production de certificats de vaccination n'ont plus de raison d'être. Le risque de complications vaccinales est de toute évidence plus grand que le risque de contracter la variole, qui est devenu nul.

[1] Org. mond. Santé Sér. Rapp. techn., 1972, N° 493.

Epidemiological notes contained in this number:
Adverse Reactions to Smallpox Vaccination, Cholera Surveillance, Imported Infections, Smallpox Surveillance, Surveillance of Foodborne Outbreaks, Tuberculosis Surveillance.
List of Infected Areas, p. 335.

Informations épidémiologiques contenues dans ce numéro:
Infections importées, réactions adverses à la vaccination antivariolique, surveillance de la tuberculose, surveillance de la variole, surveillance des poussées d'origine alimentaire, surveillance du choléra.
Liste des zones infectées, p. 335.

Plate 27.8. Cover of the *Weekly Epidemiological Record* for 26 October 1979, the day on which certification of the Horn of Africa was completed in Nairobi. The illustration shows Ali Maow Maalin, who was diagnosed as having variola minor on 26 October 1977 and was the last case in the world of endemic smallpox.

Wei-hsun, an Assistant Director-General of WHO, who was a paediatrician from Beijing, elicited the information that he had not seen a case of smallpox since 1957 and was unaware of cases anywhere in China after about 1960.

In the absence of better ways of obtaining information, two other approaches were adopted. Whenever possible, Henderson and Arita met individuals or delegations planning to visit China and told them that the Smallpox Eradication unit wished to obtain more definite information about smallpox in China. They were asked to look for facial pockmarks wherever they went and to estimate the age of any person with such pockmarks. About 15 reports were received on facial pockmarks seen in China, but without exception the persons concerned were adults—no pockmarked children were seen.

Another approach was to examine refugees from China after they had crossed the border into Hong Kong and Nepal. Arita visited Hong Kong in 1970 to request the local authorities to conduct a pockmark survey. However, although the Hong Kong health authorities originally agreed to do so, they subsequently declined, feeling that it was a politically sensitive matter. In 1975, Dr P. N. Shrestha, director of the national smallpox eradication programme in Nepal, conducted pockmark surveys among Tibetan refugees in that country, and found that 43 out of 2350 of them (1.8%) had facial pockmarks. Although they could not remember exactly when they had had smallpox, none of these people recollected that it had been contracted later than 1961 and none was less than 14 years old in 1975. The results suggested that smallpox had been eradicated in Tibet early in the 1960s.

The Consultation on the Worldwide Certification of Smallpox Eradication, held in October 1977, devoted some time to discussing the smallpox situation in China. It considered that, although according to the information available it seemed unlikely that smallpox was still endemic there, China's vast size and population—one-quarter of the world's total—justified a more detailed study. For this purpose, the Commission recommended that during 1978 China should be visited by an international commission, WHO consultants or WHO staff, to verify and document its history of smallpox eradication. This was eventually achieved in July 1979.

The problem was one of effective communications. Chinese officials, on the one hand, felt that additional documentation and a visit by Commission members were unnecessary, as transmission had been interrupted many years earlier; the Commission, on the other hand, believed that the available documentation from China was not sufficient to convince the world community of the reality of this achievement.

Because of the difficulty of obtaining the requisite information, China was (with Democratic Kampuchea, see Chapter 26) the last country to be certified by the Global Commission as being free of endemic smallpox, on 9 December 1979.

Development of Effective Contacts with China

Initial efforts, 1973–1976

At the Twenty-sixth World Health Assembly, in May 1973, the delegate from China reported that smallpox eradication had been achieved in practice by 1959 through a country-wide vaccination campaign initiated following Liberation (World Health Organization, 1973b). Extensive use had been made of part-time vaccinators and health auxiliaries in order to cover remote areas adequately. Once vaccination of the population had been completed, smallpox control had been integrated into the general health services and everyone was routinely vaccinated and revaccinated every 6 years. This had been reinforced by the recent growth of health cooperatives and the "barefoot doctor" system. No other details were given. Information on the health system in China began to emerge with the WHO study visits in 1973 and 1974, but none of these provided any specific details about smallpox, nor was there any assurance that importations from endemic neighbours to the south (Bhutan, India and Nepal) would be quickly detected and contained.

1977: Increasing urgency of better contacts

In January 1977 WHO was still no better informed about the eradication of smallpox in China and was beginning to consider seriously how to approach the problem of certification. A representative of China was invited to serve on the International Commission for the

Certification of Smallpox Eradication in Bangladesh and Burma in November–December 1977, in the expectation that the Chinese authorities might be interested in determining whether China's southern neighbours were free of smallpox. However, an invitation sent in May 1977 was declined on the grounds of "busy working arrangements". A separate invitation to participate in the October 1977 Consultation on Worldwide Certification was also refused, despite the personal attention of Dr Ch'en Wen-chieh, the Chinese Assistant Director-General of WHO who had succeeded Dr Chang Wei-hsun.

Following a request from the Smallpox Eradication unit, the WHO Regional Office for the Western Pacific cabled Beijing on 26 September 1977 and requested a brief summary statement covering the date of the last case, ongoing surveillance activities, vaccination policy and information on laboratory stocks of variola virus. The reply sent on 24 October 1977 was, if anything, briefer than the statement made by the Chinese delegation at the World Health Assembly in 1973, except that the information was given that variola virus was being held by specific institutions designated by the government. The reaction of the Chinese seemed to be one of indifference to the opinion of the rest of the world. They seemed to feel that no one need doubt their word that smallpox had been eliminated from China many years earlier.

Predictably, the Consultation in October 1977 recommended that WHO should obtain more information from China and that a visit should be arranged for a group which would include members of the Global Commission.

1978: Further informal contacts

On 4 January 1978, a letter was sent from the Regional Office for the Western Pacific proposing that 3 international experts and 3 WHO medical officers should visit China for 3 weeks during July–August 1978, and pointing out that "smallpox eradication in China appears to have been uniquely successful in terms of the vast geographical areas and methods employed. Detailed information on these activities would be of considerable value when worldwide eradication is reported to all Member States of WHO at the World Health Assembly". In order to make the proposal more readily acceptable a list of 6 experts and 5 WHO epidemiologists was attached to the letter, to enable the Chinese government to make a choice.

On 28 February 1978, following the adoption by the Executive Board of a resolution requesting the Director-General to establish the Global Commission for the Certification of Smallpox Eradication, the Chinese government was invited to nominate a member of the Commission. In their reply of 29 April, the Chinese authorities again declined to become involved in the certification process. At the same time a brief reply was received to the letter of 4 January from the Regional Office for the Western Pacific reiterating what had been stated previously concerning smallpox and adding:

> "It is based on the principle of responsibility for the health of the Chinese people and the people of the world and on the conscientious and careful conclusion reached after long years of thorough investigation and scientific surveillance that the Chinese Government has declared smallpox eradicated. As to the proposed visit to China by a group including members of the Global Commission with a purpose to 'certify' whether or not China has really achieved smallpox eradication ... I regret such a visit could not be arranged."

It was obvious that more effective communications were required between China and WHO on the philosophy of the certification programme. During the Thirty-first World Health Assembly, in May 1978, informal discussions were held between Dr Hsueh Kung-cho and other members of the Chinese delegation and WHO officials, including Arita, Chief of the Smallpox Eradication unit, at which it was agreed that the proposed visit should be postponed and that China would prepare a country report for the Global Commission before any further steps were taken. There followed a prolonged series of informal contacts aimed at convincing the Chinese authorities that the requests by WHO for more information and the invitations to participate in the certification commissions did not imply that WHO doubted their word that smallpox eradication had been achieved, but rather that it was a matter of compiling formal documentation which would convince health authorities all over the world so that it would be possible to discontinue smallpox vaccination everywhere.

Informal approaches were made during the visits to China by Dr William Foege, Director of the Center for Disease Control, Atlanta, USA, in June 1978 and by Mr Paul Lawton,

Record of the Exchange of Views at an Informal Meeting in May 1978 (I. Arita)

"Dr Hsueh Kung-cho first explained the smallpox situation in China. In 1950, special regulations to deal with the smallpox problem were set up and an eradication programme started. In 1959 the last case was recorded and to date there have been no further smallpox cases detected. Notably during the last ten years, national health programmes have been further strengthened, establishing close communication at province, country and town levels.

"I [Arita] explained the following points: Although I personally believed that smallpox had been eradicated in China, data to support this achievement were not sufficient. In the context of certification activities for global smallpox eradication, there are still a considerable number of health personnel as well as the press community who express uncertainty regarding smallpox in China. It is most desirable therefore for China to show their achievement to the world.

"In reply to this, Dr Hsueh Kung-cho indicated that a country report on surveillance activities for smallpox eradication would be prepared by China and submitted to WHO and all other necessary action required would be further reviewed when this report was prepared. In the circumstances, it was agreed that the initial proposal from WHO for Global Commission members to visit China during July–August 1978 should be postponed.

"The timing of the certification activities was discussed. The first Global Commission meeting would take place in December 1978 and the final meeting was expected to take place in October or November 1979, so that preparation of the report had to be started as soon as possible. It was agreed that the Smallpox Eradication unit would submit items to be included for special documentation during the next few days."

Division of Coordination, WHO, in October 1978. No concrete results were obtained, but the impression was gained that the Chinese authorities were becoming more open and responsive.

On 27 November 1978 WHO received a 2-page document entitled *A General Introduction on the Eradication of Smallpox in the People's Republic of China*, from Dr Chiang Yi-chen, Minister of Public Health. The only new information was that the last case had occurred in March 1960 in Yunnan Province and that variola virus was held by the National Institute for the Control of Drugs and Biological Products in Beijing.

During the meeting of the Global Commission in December 1978, Arita organized a special subcommittee to discuss this report and future plans for the certification of China, the participants being Fenner, Chairman of the Global Commission; Dr Foege, who had recently visited China; Henderson, former Chief of the Smallpox Eradication unit; Dr Kostrzewski, who had been Chairman of the International Commission for the Certification of Smallpox Eradication in India; and Dr Shrestha, who had organized the pockmark survey of Tibetan refugees in Nepal. The unanimous opinion of the subcommittee was that it was highly likely that smallpox had been eradicated in China, in view of the structure of the health and social services in the country, but that evidence was lacking; that high-level negotiations between China and WHO or influential WHO Member States on behalf of WHO would be required to obtain data; and that technically the minimum data requirement would include the results of surveys for facial pockmarks and vaccinations scars on a province-by-province basis. Dr Kostrzewski stressed the desirability of oral negotiations at the stage that had been reached; continued written requests might be perceived as intimidating. The subcommittee drafted a statement which was approved by the plenary meeting of the Global Commission and included in the Commission's report for 1978:

"Considering the extensive health service network in China and its capability for effective surveillance, the Commission expressed confidence that smallpox transmission had been interrupted. However, it was believed that more

substantial documentation would be of considerable importance to provide persuasive evidence of this fact to the world community. A more complete country report should be sought with information presented, if possible, on a province-by-province basis. Useful information would include documentation of the last cases, an account of past smallpox activities in individual provinces and current epidemiological surveillance activities indicating how suspected cases would be detected. Certification of freedom from smallpox was deferred pending receipt of additional information."

During 1978, the Global Commission certified a number of countries, including Namibia, Southern Rhodesia (Zimbabwe), and Thailand, but deferred certification of China, Democratic Kampuchea, Iraq, Madagascar and South Africa because of insufficient evidence.

1979: A visit by a WHO team is arranged

The next initiative in what had become rather delicate negotiations was undertaken, at WHO's request, by Sir Gustav Nossal, Chairman of the WHO Western Pacific Advisory Committee for Medical Research, who visited China in April 1979. He engaged in informal discussions to find out under what conditions the Chinese would accept a visit by Fenner (a fellow Australian who was Chairman of the Global Commission), accompanied by a WHO staff member. The response was encouraging. He detected a positive and flexible attitude on the part of the Chinese, who showed far less sensitivity to the issue than he had expected. The proposed visit appeared to be welcome. During the Thirty-second World Health Assembly, in May 1979, information was provided informally to the effect that the Chinese would agree to a visit by Fenner in July.

Visit of the WHO team to China

The result of these protracted negotiations was that a WHO team consisting of Fenner and Dr Joel Breman, of the Smallpox Eradication unit, visited China from 14 to 30 July 1979. They found that a country report had already been prepared by Professor Jiang Yutu, Professor Li Heming and Dr Zhao Kai, three scientists who had participated in a meeting of officials from laboratories retaining variola virus and the national control authorities concerned, which had been held

BY COURTESY OF J. BREMAN

Plate 27.9. The WHO team of J. Breman and F. Fenner, in Kunming, Yunnan Province, China, with Fu Guichen, Jiang Yutu, Jiang Weizhang and Zuo Kejia. Jiang Yutu accompanied the WHO team; the other Chinese were health officials of Yunnan Province.

The Improvement of Health Services in China

Immediately after the Liberation, one of the first acts of Mao Zedong's government was to eliminate smallpox from China by mass vaccination campaigns. This was achieved by enlisting community support and using all available health personnel for intensive vaccination campaigns (see Chapter 8). Later, routine vaccination was incorporated into primary health care. Although there had been undeniable improvements since 1949, in the early 1960s health services were still not being provided to many of the 85% of the population living in the rural areas. Mao Zedong's directive of 26 June 1965 prescribed that, in health and medical work, the stress should be put on the rural areas. The changes made were: (1) the establishment of mobile medical teams formed out of existing health manpower to work in the rural areas; (2) the discontinuation of formal medical education pending its complete reform; (3) the genuine unification of traditional and western medicine; and (4) the massive training of "barefoot doctors" and health auxiliaries for the delivery of health services to the rural population.

The Ministry of Health was reorganized and responsibility for the delivery of health services delegated to the provincial, regional or municipal level. At the same time, five-sixths of the state bureaucracy in Peking was disbanded. As a consequence of this radical decentralization, emphasis was given to the rural areas and by 1974 satisfactory coverage of the entire population had been achieved. This, however, also had the result that there was little or no epidemiological information on a country-wide basis at national level. On the other hand, comprehensive information was available at provincial and commune level.

Awareness of the need to report communicable diseases was highly developed and coverage in terms of surveillance very extensive, as even in production teams—the basic units of community organization—one person was made responsible for disease notification.

in Geneva from 23 to 24 April 1979. As others had predicted, once discussions had been established on a person-to-person basis, matters went very smoothly. The WHO team reviewed the report with the authorities as well as a special detailed report on the last outbreaks in Yunnan Province. This report also included the results of a vaccination scar and pockmark survey of 73 820 persons in the border areas of Yunnan carried out in March–May 1979. Their only real concern at the time was that, while there was comprehensive information concerning the last cases reported from Yunnan in 1960, cases had also been reported in Xizang Autonomous Region (Tibet) in 1960, about which there were no details. It was impracticable for the WHO team to visit Xizang, but the Chinese authorities promised to carry out investigations comparable to those described for Yunnan.

The WHO team, accompanied by Dr Jiang Yutu, examined the communicable disease surveillance system in three areas: Beijing municipality, Shanghai municipality and Yunnan Province, from which the last endemic case in China has been reported in 1961 (Fig. 27.15). In all areas, visits were made to provincial, municipal and district epidemic prevention sections, commune hospitals, health centres, and village primary schools. The team was impressed by the detailed records available at provincial and municipal level about smallpox outbreaks and vaccination campaigns which had been conducted well over 20 years previously. Fenner and Dr Breman felt confident that the system for the surveillance of communicable diseases operating in the country would have detected outbreaks of smallpox if they had occurred after 1960.

It was also agreed that 2 representatives from China would participate in the December meeting of the Global Commission in 1979, one of whom would be a member of the Global Commission and the other an epidemiologist familiar with the details of the eradication of smallpox in China.

The WHO team's visit as well as communications between China and WHO resulted in several documents becoming available on smallpox eradication in China, containing a great deal of data completely unknown to WHO and to the world scientific community before 1978 (WHO/SE/79.142 Rev. 1;

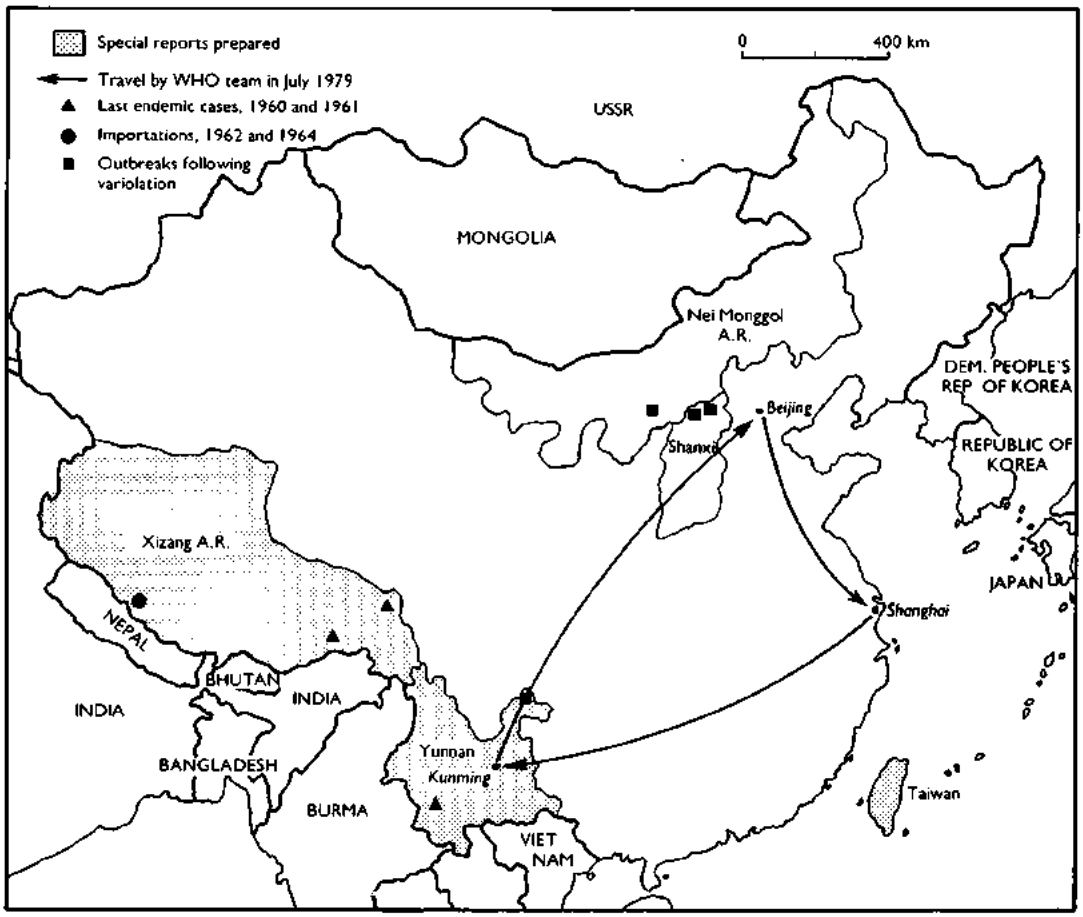


Fig. 27.15. China and neighbouring countries, in relation to certification activities, showing travel by the WHO team in July 1979 and the areas for which special reports were prepared (Provinces of Yunnan and Taiwan; Xizang Autonomous Region [Tibet]). Places where the last cases of endemic smallpox were reported in Xizang in 1960 and in Yunnan in 1961, the site of imported cases in Xizang in 1962 and 1964, and the locations of outbreaks following variolation in northern Yunnan in 1958 and in Nei Monggol Autonomous Region and Shanxi Province in 1962–1965 are also shown.

Table 27.6. China: numbers of reported cases of smallpox between 1957 and 1965, by province and autonomous region[a]

Province or autonomous region	1957	1958	1959	1960	1961	1962	1963	1964	1965
Provinces:									
Gansu	1	0	0	0	0	0	0	0	0
Henan	0	1	0	0	0	0	0	0	0
Shanxi	0	0	0	0	0	0	28[b]	0	4[b]
Sichuan	108	0	0	0	0	0	0	0	0
Yunnan	92	661	476	7	28	0	0	0	0
Autonomous regions:									
Nei Monggol	0	0	0	0	0	1[b]	225[b]	30[b]	0
Xinjiang	114	9	0	0	0	0	0	0	0
Xizang (Tibet)	0	0	0	16	0	1[c]	0	5[c]	0
Total	315	671	476	23	28	2	283	35	4

[a] Data for all provinces, autonomous regions and municipalities over the period 1950–1965 are shown in Chapter 8, Table 8.13. No cases were reported after 1956 in the administrative units not listed. No cases were reported anywhere in China after 1965.

[b] Associated with variolation.

[c] Importations from Nepal.

WHO/SE/79.151; SME/79.10; SME/79.11, Fenner & Breman). Subsequently, Xu & Jiang (1981) described the elimination of smallpox from Shanghai, and Jiang Yutu published an account of smallpox in China in a Chinese medical encyclopaedia (Jiang, 1985). The description of the eradication of smallpox in China given in Chapter 8 is based on the relevant information in these reports. Three matters of particular importance for the certification programme are described below: smallpox in Yunnan Province and in Xizang Autonomous Region (Tibet), and the location of laboratory stocks of variola virus. Also included in the present chapter is an account of outbreaks of smallpox in northern China in 1962–1965, which did not come to the attention of WHO until the 1980s. The data are shown in Table 27.6.

Smallpox in Yunnan Province

Yunnan, with a population of about 30 million, is situated in south-western China and borders on Burma, the Lao People's Democratic Republic and Viet Nam (Fig. 27.16). Although the reported incidence of smallpox had been reduced to zero throughout most of China by the late 1950s (see Chapter 8, Table 8.13), cases continued to occur in Yunnan until 1961 (Table 27.7). Scattered cases were reported from counties in many parts of Yunnan up to 1959, but after that year 5 out of the 6 outbreaks reported occurred in counties adjacent to Burma (Fig. 27.16). The villages in these counties were inhabited by ethnic minorities having strong ties with Burma and there was frequent communication with villages across the border. At the time, communications between these areas and Kunming, the provincial capital, were very poor, and elements of the Kuomintang, by preventing adequate vaccination coverage, had increased the difficulty of eliminating smallpox. Up to 1960, smallpox outbreaks repeatedly occurred on the Burmese side of the border and the disease then passed over into China as the inhabitants carried it across. For example, in 73 of the 461

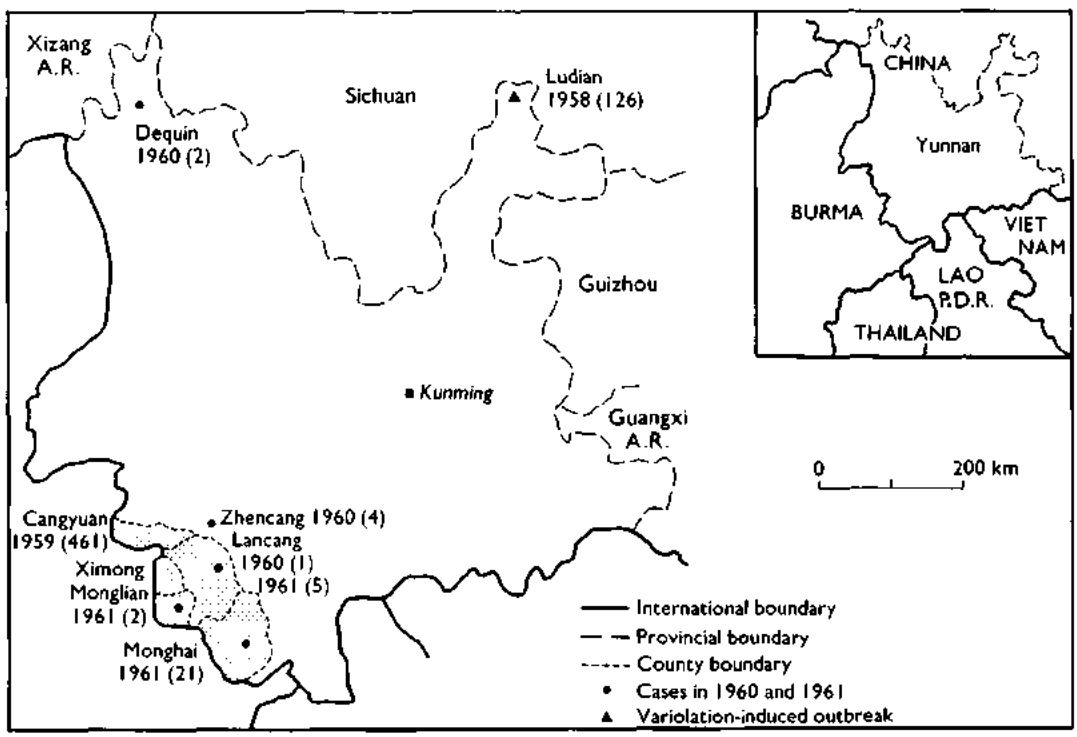


Fig. 27.16. Yunnan Province, showing sites of smallpox outbreaks in 1960–1961 and counties near the Burmese border where vaccination scar and facial pockmark surveys were conducted in 1979. An outbreak of 461 cases occurred in Cangyuan county in 1959 and a variolation-induced outbreak of 126 cases occurred in Ludian county in northern Yunnan in 1958. Numbers next to locations indicate the year in which the number of cases (in parentheses) occurred.

cases (16%) reported in 1959 from Cangyuan county, the disease had been contracted in Burma. It was estimated that at this time between 30% and 60% of the villagers on the Chinese side of the border were vaccinated. After a delayed but intensive vaccination campaign in Cangyuan and neighbouring counties in 1959, which was said to have reached 98.8% of the population, the outbreaks subsided. Seven cases were reported from 3 counties in 1960 and 28 cases in 1961, 5 from Lancang county, 21 from Monghai county, and finally 2 from Monglian county—the last endemic cases in China.

In the border districts in which the last smallpox outbreaks had occurred, vaccination scar and pockmark surveys were conducted in March–May 1979, in preparation for the visit to Kunming by the WHO team. The overall vaccination rate among 44 771 persons examined in the rural districts was 90.4%, compared with 94.0% for Kunming municipality (Table 27.8). In both areas, the rate was also satisfactory for the age group 0–4 years. The overall frequency of pockmarks in persons in these districts was 6.0%, compared with 0.3% in Kunming municipality (Table 27.9), but the age distribution (Table 27.10) revealed that in Monglian county, in which, as has already been mentioned, the last reported cases occurred in 1961, no person under 22 years of age had facial pockmarks, nor were any pockmarked persons under 20 found elsewhere in Yunnan.

The evidence provided to the Global Commission showed that endemic smallpox had persisted in these remote border areas of Yunnan for several years after it had been eliminated from the rest of China (except Xizang Autonomous Region; see below). However, the pockmark and vaccination scar surveys conducted in 1979 in the counties in which smallpox was last endemic provided reassurance that transmission had been interrupted in the early 1960s and that no further outbreaks had occurred.

Table 27.7. Yunnan Province: numbers of reported cases of smallpox, 1958–1962, by county[a]

County	1958	1959	1960	1961	1962
Baoshan	1	0	0	0	0
Cangyuan	0	461	0	0	0
Deqing	0	0	2	0	0
Fuyuan	25	0	0	0	0
Gujing	1	0	0	0	0
Lancang	0	1	1	5	0
Ludian	126[b]	0	0	0	0
Luquan	18	0	0	0	0
Luxi	0	1	0	0	0
Monghai	0	0	0	21	0
Monglian	126	2	0	2[c]	0
Xiangyun	0	1	0	0	0
Zhenkang	0	0	4	0	0
Zondian	0	10	0	0	0
Unknown	364	0	0	0	0
Total	661	476	7	28	0

[a] Data from Dr Jiang Yutu (personal communication, 1985).
[b] Outbreak caused by variolation given by nasal insufflation.
[c] The last cases of endemic smallpox in China.

Smallpox in Xizang Autonomous Region (Tibet)

Xizang Autonomous Region (Fig. 27.17) is separated from the neighbouring countries of Bhutan, India and Nepal by the Himalayan mountain chain. Its 1.8 million inhabitants are spread over 1.2 million square kilometres, giving a population density of only 1.5 per square kilometre. Xizang therefore appears to have been a rather unfavourable place for maintaining smallpox transmission, although

Table 27.8. Yunnan Province: results of vaccination scar survey among rural and urban populations, March–May 1979, by age group

Age group (years)	Rural population[a]			Urban population[b]		
	Number of persons observed	Persons with vaccination scar		Number of persons observed	Persons with vaccination scar	
		Number	%		Number	%
0–4	8 021	6 228	77.6	773	688	89.0
5–19	21 646	20 482	94.6	12 323	11 412	92.6
≥20	15 104	13 746	91.0	7 006	6 806	97.1
Total	44 771	40 456	90.4	20 102	18 906	94.0

[a] Cangyuan, Monghai, Monglian and Ximong counties.
[b] Kunming municipality.

Table 27.9. Yunnan Province: results of facial pockmark survey in counties near the border with Burma, and Kunming municipality, March–May 1979

County or municipality	Number of persons observed	With facial pockmarks	
		Number	%
Cangyuan	9 047	767	8.5
Lancang	7 885	140	1.8
Menglian	7 157	256	3.6
Ximeng	2 174	420	19.3
Total for counties	26 263	1 583	6.0
Kunming municipality	20 102	57	0.3

Table 27.10. Yunnan Province: age distribution of 1020 pockmarked persons, May 1979

Age group (years)	Number of persons with pockmarks[a]	
	Menglian county (7157 subjects)	Neighbouring counties (19 106 subjects)
0–19	..	0
⩾20	..	764
0–21	0	..
22–29	64	..
30–39	63	..
40–49	62	..
50–59	36	..
⩾60	31	..

[a] None of whom had had smallpox after 1960; ..=data not recorded.

it was periodically subject to epidemics of great severity. In all, 23 cases were reported in 1955 and 4 in 1956, followed by 16 in 1960. This led to a request from the WHO team for a special report, which was forwarded to WHO in November 1979. No further details of the cases in 1960 were available except that 5 of them occurred in Changdu subregion and 11 in Lhasa subregion.

The special report provided details of subsequent vaccination coverage, information on suspected cases of smallpox, and the results of vaccination scar and facial pockmark surveys conducted in August 1979. Between 1960 and 1979, 39 cases of suspected smallpox were investigated in the 3 years 1963, 1965 and 1970. All turned out to be cases of chickenpox. At the time of the Global Commission meeting, the Chinese authorities reported rumours of 4 importations from Nepal into Xizang in the early 1960s, with 1 secondary case. Subsequently Dr Jiang Yutu (personal communications, 1984, 1985) confirmed that, following importations from Nepal, 1 case had occurred in Nielamu county (Rikeze subregion) in 1962 and 5 cases in 1964.

In addition to routine vaccination, for which freeze-dried vaccine was used from 1965 onwards, mass vaccination campaigns were carried out in 1964 and 1975 to increase the immunity level of the population in areas bordering on India and Nepal. Limited data showed that the take rate in persons undergoing primary vaccination varied between 86% and 95%.

The vaccination scar and facial pockmark surveys in August 1979 covered 15 661 persons in Shannan and Rikeze subregions and Lhasa City (Table 27.11). Vaccination rates were high (91%) among those over 4 years of age but only 57.5% in those below that age. No persons with facial pockmarks were found in Shannan subregion but about 1% of over 12 000 persons examined in Lhasa City and Rikeze subregion, all of them over the age of 20 years, were pockmarked. This evidence reinforced the data from the pockmark survey on Tibetan refugees provided to WHO earlier.

Province of Taiwan

In 1972, WHO decided to follow the United Nations in recognizing the Beijing government as representing China, considering Taiwan as one of its provinces and referring to the island as "China (Province of Taiwan)".

Unlike mainland China, Taiwan had been an active member of WHO from 1948, when the Organization was established, until 1972, when it was excluded following the above-mentioned decision. In 1978, Taiwan had a population of 17.9 million (7.5 million in 1950) and a comprehensive health services infrastructure. The last big epidemic of smallpox had occurred in 1946–1947: 6754 cases with 2040 deaths. Mass vaccination campaigns with the annual primary vaccination of infants and vaccination of the entire population eliminated endemic smallpox in 1954, after which no cases had been found. The country report, endorsed by the Director-General of Health Services, together with a signed "Declaration of Smallpox-free Status", was judged to be satisfactory by the Global Commission on 8 December 1978, but for purposes of formal certification Taiwan could, of course, only be considered together with China as a whole.

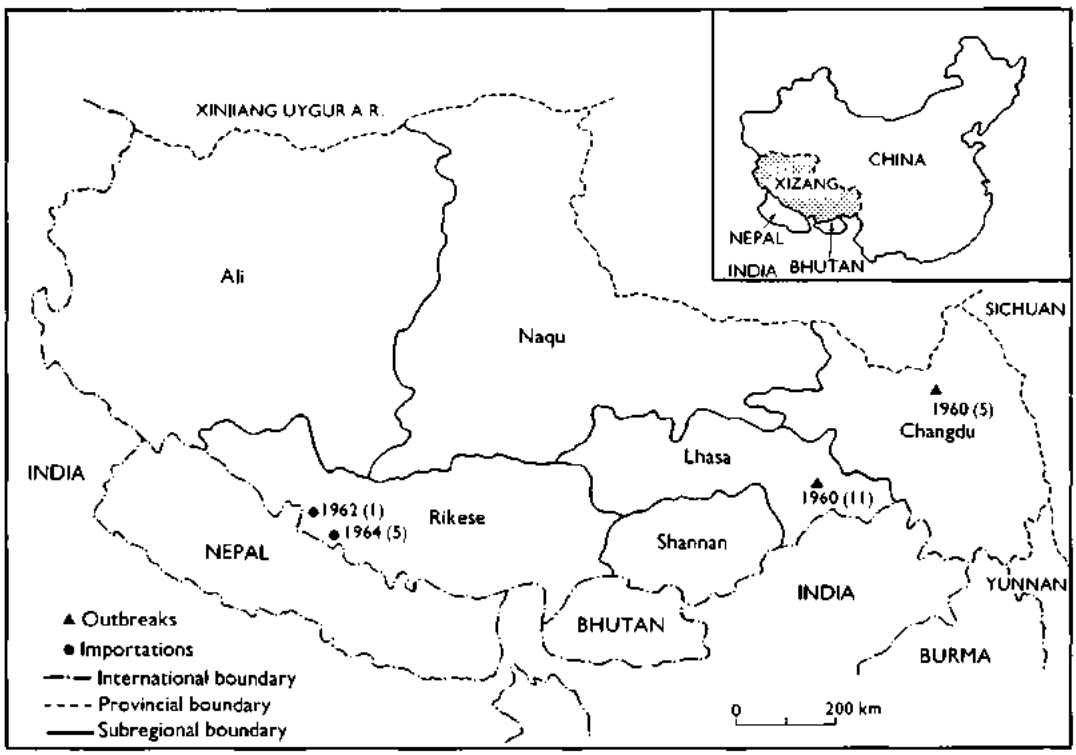


Fig. 27.17. Xizang Autonomous Region (Tibet), showing subregional, provincial and international boundaries, and the sites where the last endemic cases occurred in 1960: 5 cases in Changdu county (Changdu subregion) and 11 cases in Linzki county (Lhasa subregion). There was 1 case in 1962 and 5 cases in 1964 in Nielamu county (Rikese subregion), associated with importations from Nepal. Numbers next to locations indicate the year in which the number of cases (in parentheses) occurred.

Table 27.11. Xizang Autonomous Region (Tibet):[a] age-specific vaccination scar and facial pockmark rates, August 1979

Age group (years)	Number examined	Number with vaccination scars	Rate (%)	Number with pockmarks	Rate (%)
0–4	1 231	708	57.5	0	0
5–19	8 715	7 944	91.2	0	0
⩾20	5 715	5 220	91.3	125	2.2
All ages	15 661	13 872	88.6	125	0.8

[a] Shannan and Rikeze subregions and Lhasa City.

Variolation in China after 1950

Variolation, initially by insufflation and later by scarification, had been practised in China since about the 10th century (see Chapter 6), and was practised almost as widely as vaccination during the early years of the 20th century. It continued to be used for over a decade after the Liberation in remote rural areas that were at the time served almost exclusively by practitioners of traditional medicine. The Global Commission was told of an outbreak of 126 cases in 1958 in Ludian county in the north-east corner of Yunnan Province (see Fig. 27.16) which followed variolation by nasal insufflation, 5 years after the last case of endemic smallpox in that county but only a year after the last outbreaks in other counties in northern Yunnan.

Some years after the last meeting of the Global Commission, information was provided by Dr Jiang Yutu (1985; and personal communications, 1984, 1987) about other variolation-induced outbreaks in northern China in the mid-1960s (Fig. 27.18), in Nei Monggol Autonomous Region (1 case in

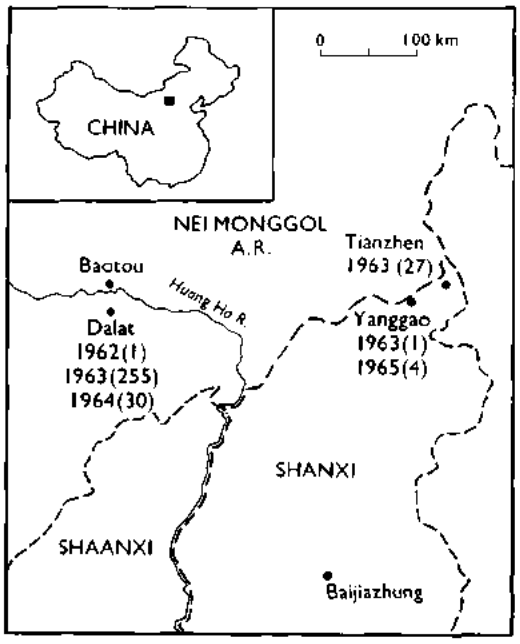


Fig. 27.18. Sites of the outbreaks in northern China, 1962–1965, following variolation. Figures beneath place names indicate the year of the outbreak and the number of cases (in parentheses). (From Jiang Yutu, 1985; and personal communications, 1984, 1987.)

1962, 255 cases in 1963 and 30 cases in 1964) and 2 nearby counties of Shanxi Province (28 cases in 1963 and 4 in 1965).

These incidents have been explained by Dr Jiang Yutu (personal communications, 1984, 1987) as follows. Throughout the whole of continental China between 1959 and 1962, almost everything, including smallpox vaccine, was in short supply. In 1963, just after the country had recovered from this situation, people demanded that their children should be vaccinated but supplies of potent vaccine were not sufficient to ensure the coverage of all areas, especially the mountainous and remote ones. In Nei Monggol and Shanxi, as a result, the inhabitants turned to their local traditional doctors, some of whom had been variolators, maintaining virus in sealed jars containing honey. After smallpox had disappeared from their region in the 1950s (see Chapter 8, Table 8.13), they had continued to maintain the viability of the virus by the annual inoculation of their own children. Thus, when supplies of vaccine failed in the early 1960s, these variolators still had active variola virus, and with the cessation of vaccination many more children became susceptible and many more were inoculated with the virus. The outbreaks which then occurred were investigated by Dr Zhao Kai, of the National Vaccine and Serum Institute, Beijing, who recovered variola virus both from cases and from the variolation material. Stringent measures were taken to eliminate the practice and supplies of potent freeze-dried vaccine were provided to remove any need for recourse to variolation. As has been pointed out earlier, a massive reorganization of the health services in China in 1965 greatly improved the quality of health care in the rural areas. No cases of smallpox occurred after 1965, either in these areas or elsewhere in China.

Variola Virus Stocks

Inquiries made by the Chinese Ministry of Health in 1961–1962, 1966 and again in 1978 established that the only variola virus stocks held in laboratories were located in the National Institute for the Control of Biological Products in Beijing. The virus had last been used in 1967, as a positive control during laboratory investigations of material from a suspected case of smallpox. The WHO team noted:

"The laboratory does not conform to WHO standards for facilities storing variola virus. As a depository only, the physical and administrative arrangements seem adequate for the particular situation, but the building housing the virus stocks, and the cabinet itself, would not offer maximum security against a determined saboteur."

In January 1981 these stocks were destroyed by the Chinese government.

Review by the Global Commission

WHO's efforts to collect additional information on smallpox in China had eventually resulted in a visit of a team of experts to the country in July 1979 and the accumulation of substantial data that lent support to the view that smallpox had been eradicated. However, there was little time left for review and assessment of these data by the Global Commission, since the target date for global certification was the end of 1979. On 21 August 1979, Arita wrote to members of the Global Commission and submitted to them all the data then available: the country report by the Ministry of Health (WHO/SE/79.142

Rev. 1); a provincial report by the Health Department of Yunnan Province, in which the last endemic case had occurred (SME/79.10); a report on the visit to China by Fenner and Breman (SME/79.11); and a report on smallpox eradication in Taiwan Province. Information on Xizang (Tibet) and vaccine production arrangements did not become available to WHO until November 1979. In the letter, Arita noted that the WHO team believed, from the evidence that it had been able to collect on its visit, that smallpox had been eliminated from China, and specifically requested an answer to the following 3 questions:

(1) Do you think that the Global Commission should now approve certification of smallpox eradication in China?; or

(2) Do you as an individual member of the Global Commission approve certification of smallpox eradication in China, but feel that its final eradication should not be declared until all the Commission members meet again from 6 to 9 December 1979?; or

(3) Do you have any other comments or recommendations which do not fall into the above two categories?

The response of the members of the Global Commission was equivocal; 8 advocated immediate certification, 5 wished to discuss it at the December meeting, and 6 did not reply. Dr Holger Lundbeck, a Commission member from Sweden, expressed a widely held view by saying that, while he had no doubt that smallpox transmission had been interrupted long ago in China, in order to convince the world community, more information should be sought about Xizang for "there will always be people who doubt that eradication has been achieved, in particular in countries as big as China".

Consideration of the certification of smallpox eradication in China was therefore deferred until the meeting of the Global Commission in Geneva in December 1979, which was attended by Dr Zhang Yi-hao from China as a member and Dr Jiang Yutu as an adviser. In addition to the reports previously circulated, 2 further reports were then available: (1) *Supplementary Report about the Eradication of Smallpox in China*, sent to WHO on 17 November 1979 by the Minister of Public Health, Dr Qian Xinzhong, which provided information on the production of smallpox vaccine, the health service structure, and the quarantine services; and (2) a report (WHO/SE/79/151) which included details of vaccination campaigns and coverage in Xizang, the last outbreaks there, and the results of a pockmark survey carried out in August 1979, which has already been described. Having considered all the data and heard reports from Dr Zhang Yi-hao and Dr Jiang Yutu, the Commission certified China to be free of smallpox on 9 December 1979.

CONCLUSIONS

In every health programme, success depends not only on the scientific technology but also on the managerial arrangements and political negotiations which pave the way for its implementation. The certification activities in the Horn of Africa and China illustrate how scientific technology and managerial and political arrangements were developed in parallel in order to accomplish a single task.

With the certification of the Horn of Africa and China, the chapter on the certification of the global eradication of smallpox, which had commenced in 1971 when Brazil recorded the last case on the South American continent, was closed. Activities had been greatly intensified since 1976 when it became apparent that global eradication was imminent. Four years of effort, from 1976 to 1979, had been successful in confirming that the world had become free of smallpox. This was the first time in history that human efforts had succeeded in eliminating a disease—and one which had been feared for thousands of years. Neither the vigorous operational campaign for the eradication of the disease nor the diligent certification programme was free from technical and human errors. Nevertheless, both were eventually successful.

The Global Commission met in Geneva from 6 to 9 December 1979. It had before it a draft final report which had already been reviewed and revised by 12 members of the Commission in Nairobi in October. The meeting concentrated its attention on the conclusions and recommendations (World Health Organization, 1980). After 4 days of intensive discussions, it accepted the following conclusions:

(1) Smallpox eradication had been achieved throughout the world.

(2) There was no evidence that smallpox would return as an endemic disease.

L. BANCO

Plate 27.10. Members of the Global Commission for the Certification of Smallpox Eradication, 9 December 1979. *From left to right, front row:* S.S. Marennikova (USSR), J. Azurin (Philippines), P.N. Burgasov (USSR), F. Fenner (Australia; Chairman), J. Kostrzewski (Poland; Vice-Chairman), D.A. Henderson (USA), W. Koinange (Kenya), Zhang Yihao (China); *back row:* P.F. Wehrle (USA; Rapporteur), R.N. Basu (India), J.M. Aashi (Saudi Arabia), H.B Lundbeck (Sweden), B.A. Rodrigues (Brazil), K.R. Dumbell (United Kingdom), R. Netter (France), I. Tagaya (Japan), J.S. Moeti (Botswana), Kalisa Ruti (Zaire), P.N. Shrestha (Nepal), A. Deria (Somalia).

The 19 recommendations covered all aspects of operations relevant to orthopoxviruses and the diseases that they cause in a world from which smallpox had been eradicated. The meeting closed on 9 December 1979 with a ceremony in which the members of the Global Commission signed a parchment declaring that the world was free of smallpox (see frontispiece).

The final report of the Global Commission, *The Global Eradication of Smallpox* (World Health Organization, 1980), was published in the 6 official languages of the World Health Organization and its conclusions and recommendations were accepted without change by the Thirty-third World Health Assembly on 8 May 1980.

CHAPTER 28

POST-ERADICATION OPERATIONS: IMPLEMENTATION OF THE RECOMMENDATIONS OF THE GLOBAL COMMISSION

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INTRODUCTION

In order to convince the world community that smallpox had indeed been eradicated globally, WHO developed a comprehensive and sophisticated system for the certification of smallpox eradication, culminating in the final meeting in December 1979 of the Global Commission for the Certification of Smallpox Eradication (see Chapter 24). The Global Commission foresaw that the certification of eradication was not enough in itself—steps would have to be taken over the ensuing years to maintain public confidence in the reality of eradication and to ensure that advantage was rapidly taken of the benefits of the achievement, such as the ending of vaccination against smallpox. With this aim in view, the Commission's final report (World Health Organization, 1980) listed 19 recommendations indicating the activities to be undertaken during the years following the declaration by the Thirty-third World Health Assembly on 8 May 1980 that smallpox had been eradicated throughout the world.

The 19 recommendations made by the Global Commission were unanimously endorsed by the World Health Assembly on the same date (resolution WHA33.4). They dealt with post-eradication policies under 8 headings: (1) smallpox vaccination policy; (2) reserve stocks of vaccine; (3) investigation of suspected cases of smallpox; (4) laboratories retaining variola virus stocks; (5) human monkeypox; (6) laboratory investigations; (7) documentation of the smallpox eradication programme; and (8) WHO Headquarters staff.

Concurrently with the declaration of the global eradication of smallpox the Global Commission was dissolved, and in 1981 a new 6-member committee—the Committee on Orthopoxvirus Infections—was established by the Director-General of WHO. Its membership was drawn from the Global Commission, whose chairman, Fenner, also became chairman of the Committee. Except in 1985, this Committee met annually in Geneva from 1981 to 1986, critically reviewed the progress made in the post-smallpox-eradication programme and advised WHO on the implementation of the Global Commission's recommendations. The Committee was serviced and the implementation of post-eradication activities supervised by the Smallpox Eradication unit, which continued to exist, though with a reduced staff (consisting of 3, later 2, medical officers, an operations officer and support staff), all of whom had had extensive experience in the eradication programme. In the regional offices, all activities related to the post-eradication programme were transferred to the general programme of disease control and prevention or to the Expanded Programme on Immunization.

In this chapter, the post-eradication programme activities carried out between 1980 and 1986 are described, each of the 8 groups of recommendations being considered in turn. Each section is preceded by the relevant statement from the final report of the Global Commission (World Health Organization, 1980) together with the corresponding recommendations.

VACCINATION POLICY

"*Smallpox vaccination of the general public.* As smallpox has been eradicated, smallpox vaccination is no longer justified. Because vaccination may result in serious complications, which are occasionally fatal, no one except investigators at special risk should be vaccinated in any country including those where monkeypox cases have occurred.

"*Recommendation (1).* Smallpox vaccination should be discontinued in every country except for investigators at special risk.

"*Smallpox vaccination certificates for international travellers.* With the certification of global eradication of smallpox, no country should now require vaccination certificates from international travellers.

"*Recommendation (2).* International certificates of vaccination against smallpox should no longer be required of any travellers."

Routine Vaccination Programmes

In North America and in many countries of Europe and the Western Pacific Region, routine vaccination programmes had ceased before recommendation (1) was made (Table 28.1).

The health administrations of countries in other regions, however, weighed the risks and benefits of smallpox vaccination in the light of the progress made with the global smallpox eradication programme. In previously endemic countries, international commissions for the certification of smallpox eradication had recommended that vaccination programmes

Table 28.1. Number of countries carrying out vaccination against smallpox, by WHO region, 1976–1985[a]

WHO region	Number of countries[b]	Year									
		1976	1977	1978	1979	1980	1981	1982	1983	1984	1985
Africa	44	44	43	43	32	11	1	1	0	0	0
Americas	33	27	27	25	25	22	0	0	0	0	0
South-East Asia	11	11	11	11	10	4	1	1	0	0	0
Europe	34	27	23	21	18	6	3	2	2	2	0
Eastern Mediterranean	23	22	21	16	12	6	2	1	0	0	0
Western Pacific	19	10	8	7	6	3	0	0	0	0	0
Total	164	141	133	123	103	52	7	5	2	2	0

[a] The figures are those for the end of each of the years in question.
[b] Based on the membership of WHO of the countries in the different WHO regions as at January 1984.

should be maintained until global eradication had been certified. When this occurred, in May 1980, these programmes were soon curtailed or discontinued, particularly in countries that depended on WHO for their supplies of vaccine. Of the 156 Member States of WHO at that time, 52 were still conducting routine smallpox vaccination programmes at the end of 1980, but by the end of 1983 this number had been reduced to 2—namely, Albania, in which both primary vaccination and revaccination continued to be performed, and France, in which only revaccination was recommended. Both these countries stopped all routine vaccination in 1984.

The official discontinuation of routine vaccination programmes, however, did not always mean that vaccination had ceased altogether. In many countries, both developed and developing, appropriate instructions were not always effectively promulgated by the central health administration, and local vaccination programmes sometimes continued to be conducted. The distribution of vaccine could be readily controlled in countries in which production was carried out in national laboratories, but such control was more difficult in those in which private companies produced vaccine and sold it on request. In the USA, a few cases of severe complications (e.g., eczema vaccinatum and progressive vaccinia) occurred when vaccinia virus was used for the treatment of herpes simplex, a form of therapy with a long history but one whose effectiveness was open to question. Eventually, agreement was reached in the USA in 1984 that, apart from making provision for the armed services, the producer would restrict the supply of smallpox vaccine to the Centers for Disease Control, for use by laboratory workers where indicated. By means of announcements in the *Weekly epidemiological record* and communications with governments, WHO intervened several times to advise that vaccination programmes should be stopped, stressing the risk of complications. In addition, in 1983, the Smallpox Eradication unit contacted all vaccine producers to urge that no vaccine should be made available for civilian use.

Although routine vaccination of the general public was speedily abandoned in most countries, military personnel continued to be vaccinated. As a result, incidents occurred in several countries in which a newly vaccinated recruit infected a close contact, often in the home (Laboratory Centre for Disease Control, 1981; *Morbidity and mortality weekly report*, 1984; *Journal of the American Medical Association*, 1985). Although on scientific grounds the vaccination of military personnel could have been discontinued at the same time as that of the civilian population, decisions whether or not to do so were based on political considerations, and WHO could do little to influence them. However, as time went on, an increasing number of countries discontinued the vaccination of military personnel. In order to prevent accidental vaccinial infections of civilians, the WHO Committee on Orthopoxvirus Infections recommended in 1984 that "military personnel who have been vaccinated be confined to their bases and prevented from contacting unvaccinated persons for a period of two weeks following vaccination" (WHO/SE/84.162). This recommendation was made known to all Member States. Reviewing the situation in March 1986, the Committee on Orthopoxvirus Infections rec-

ommended that "smallpox vaccination to protect military personnel against the disease be terminated" (*Wkly epidem. Rec.*, 1986b).

Recommendation (1) exempts only "investigators at special risk" from the recomendation that vaccination should be discontinued. This group includes the following 3 categories: (1) Investigators who handle variola or monkeypox virus in a laboratory—a very small group. Everyone who enters such laboratories should undergo regular annual or triennial vaccination. (2) Investigators who work with other orthopoxviruses that are infectious for man (vaccinia and cowpox viruses). Triennial vaccination of those who handle such viruses is recommended. (3) Special surveillance teams investigating cases of human monkeypox in Zaire. At the present time, vaccination of the general population in areas in which human monkeypox virus is present is not recommended, on the grounds that the risk of monkeypox infection does not warrant either the cost of vaccination or its risks. In all, the number of persons for whom smallpox vaccination is still recommended is very small, amounting to only a few hundred persons throughout the world.

Vaccination Certificates for International Travel

At the beginning of 1980, 23 of the 155 countries for which information was available still required international travellers to hold an international certificate of vaccination against smallpox. In May 1981 the Thirty-fourth World Health Assembly formally struck smallpox from the International Health Regulations and in 1983 the new edition of the International Certificates of Vaccination no longer contained any pages for smallpox vaccination (Plate 28.1).

After the declaration of the global eradication of the disease, the number of countries officially requiring international travellers to hold a certificate of vaccination against smallpox quickly decreased to only 2 (Chad and Democratic Kampuchea) in 1981 and to none in 1982. These figures are based on the reports

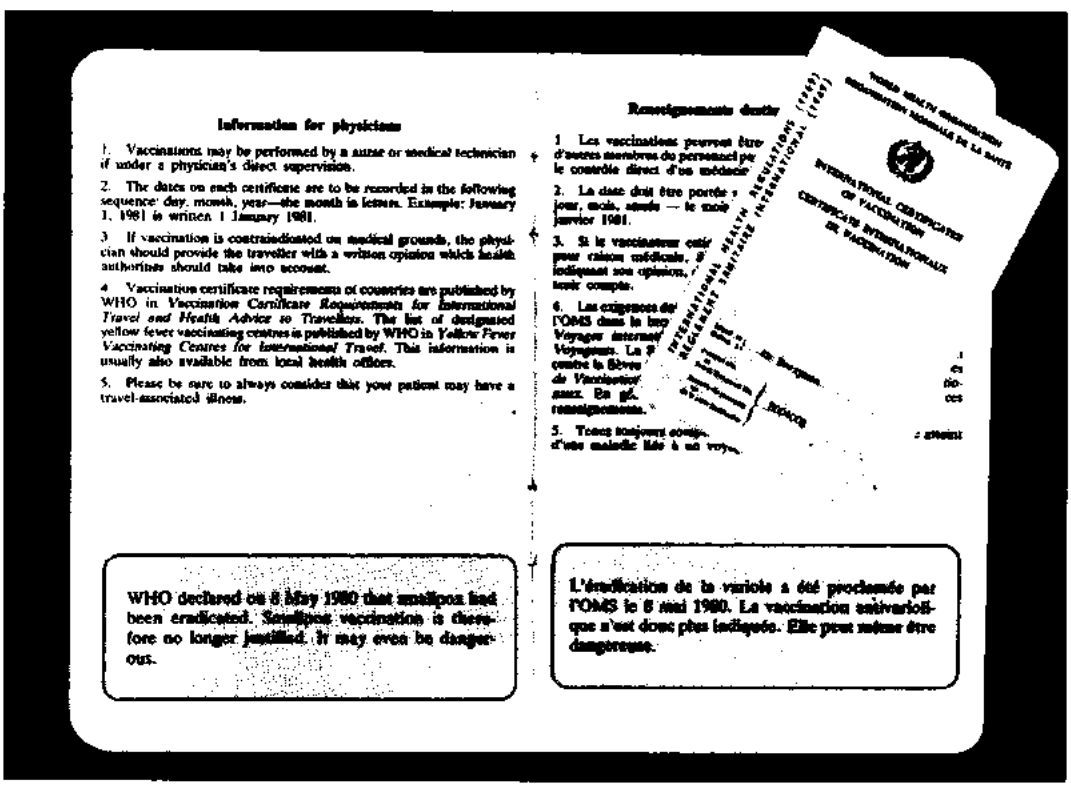
Information for physicians
1. Vaccinations may be performed by a nurse or medical technician if under a physician's direct supervision.
2. The dates on each certificate are to be recorded in the following sequence: day, month, year—the month in letters. Example: January 1, 1981 is written 1 January 1981.
3. If vaccination is contraindicated on medical grounds, the physician should provide the traveller with a written opinion which health authorities should take into account.
4. Vaccination certificate requirements of countries are published by WHO in *Vaccination Certificate Requirements for International Travel and Health Advice to Travellers*. The list of designated yellow fever vaccinating centres is published by WHO in *Yellow Fever Vaccinating Centres for International Travel*. This information is usually also available from local health offices.
5. Please be sure to always consider that your patient may have a travel-associated illness.
WHO declared on 8 May 1980 that smallpox had been eradicated. Smallpox vaccination is therefore no longer justified. It may even be dangerous.
INTERNATIONAL CERTIFICATE OF VACCINATION
CERTIFICAT INTERNATIONAL DE VACCINATION
L'éradication de la variole a été proclamée par l'OMS le 8 mai 1980. La vaccination antivariolique n'est donc plus indiquée. Elle peut même être dangereuse.
WHO

Plate 28.1. The 1983 version of the International Certificate of Vaccination. It no longer contains any pages for smallpox vaccination but includes a statement that it is no longer justified.

to WHO of national health administrations, but in fact during the first few years of the 1980s international travellers were sometimes asked for certificates of smallpox vaccination by health officers at ports or airports or by consulates when they applied for visas, or were informed that they would need certificates by those through whom they arranged their travel. This occurred in developed as well as developing countries, both because of poor communications between the ministries of health and other national authorities, such as ministries of foreign affairs and their representatives abroad, and because of the difficulty of ensuring that travel agencies were properly informed and gave correct advice to their clients. Following repeated interventions by WHO, the number of such incidents gradually diminished and by 1984 only a few occurred.

RESERVE STOCKS OF VACCINE

"Although human-to-human transmission of smallpox has been interrupted everywhere and the Global Commission believes that the likelihood of reintroduction of smallpox from laboratories or natural or animal reservoirs is negligible, it is prudent for WHO and national health authorities to be prepared for unforeseen circumstances. One measure that should be taken is to ensure that adequate reserves of potent freeze-dried vaccine are available. This vaccine should be stored at −20 °C and its potency periodically checked. Seed lots of vaccinia virus for the future preparation of vaccine should be maintained, and stocks of bifurcated needles should be available.

"*Recommendation* (*3*). Sufficient freeze-dried smallpox vaccine to vaccinate 200 million people should be maintained by WHO in refrigerated depots in two countries, together with stocks of bifurcated needles.

"*Recommendation* (*4*). The stored vaccine should be periodically tested for potency.

"*Recommendation* (*5*). Seed lots of vaccinia virus suitable for the preparation of smallpox vaccine should be maintained in designated WHO collaborating centres.

"*Recommendation* (*6*). National health authorities that have vaccine stocks should be asked to inform WHO of the amount of vaccine maintained."

WHO Reserve Stocks of Vaccine

In December 1980, the Smallpox Eradication unit drew up detailed procedures for implementing recommendations (3) and (4); these were set out in a document entitled *Management of reserve stocks of vaccine in the post-smallpox eradication era* (WHO/SE/80.158 Rev.1), which was approved by the WHO Committee on Orthopoxvirus Infections in March 1981. The recommended storage temperature of −20 °C or lower was based on previous experience in the potency testing of batches of vaccine produced in the Connaught Laboratories, Canada; the Lister Institute, United Kingdom; the National Institute of Public Health, Netherlands; the Swiss Serum Institute, Switzerland; and Wyeth Laboratories, USA (Table 28.2). These batches had been stored at temperatures ranging from +4 °C to −20 °C over a period of 8–13 years. The potency of the great majority had remained at an adequate level, and it was

Table 28.2. Smallpox vaccine titres[a] after long-term storage: typical results from laboratories in 4 countries

Country and batch number	Year of manufacture	Original titre[b]	Storage temperature	Storage period (years)	Titre on retesting
Canada:					
1517-12	1971	..	4 °C	8	8.1
Switzerland:					
L4695	1966	8.0	−20 °C	10	8.0
United Kingdom:					
701	1963	8.0	−15 °C	13	7.9
USA:					
177501	1963	..	5 °C for 7 years; −20 °C for 4 years	11	8.2

[a] Expressed as $\log_{10}$ pock-forming units per ml of reconstituted vaccine.
[b] .. = data not available.

assumed that storage at a temperature of −20 °C would suffice to maintain a satisfactory titre for many years.

At the end of 1980, 68 million doses of vaccine were stored in Geneva and 6 million doses in New Delhi. These stocks had been donated by 9 countries—Belgium, Canada, the German Democratic Republic, India, the Islamic Republic of Iran, the Netherlands, Sweden, the USSR and the USA—India and the USSR being the major donors. Between 1981 and 1985, further donations were made by Belgium, India and the USSR, but some stocks were destroyed (see below), so that the total reserve stocks at the end of 1985 amounted to 5 034 178 vials, in 459 batches. If bifurcated needles were to be used, this amount of vaccine would be sufficient to vaccinate some 300 million persons. About 3.7 million bifurcated needles are also stored in Geneva.

These stocks can be made available for any country needing to undertake emergency containment measures, but only if a presumptive diagnosis of smallpox has been confirmed by expert clinical and laboratory investigations (see below).

Testing

Batches of vaccine will continue to be sampled periodically for as long as the WHO reserve is maintained, in accordance with the procedure laid down in document WHO/SE/80.158 Rev. 1; in this way the potency of all batches can be regularly monitored so that any decline in potency can be detected without delay.

Testing is carried out by the National Institute of Public Health, Bilthoven, Netherlands, which remains the WHO International Collaborating Centre for Smallpox Vaccine. In order to ensure that the data are comparable with those obtained in previous years, the Institute has decided to continue potency testing by pock counting on the chorioallantoic membrane, rather than by the newer and somewhat more accurate technique of plaque assay.

Problems encountered

The problems encountered during the implementation of the recommendations regarding reserve stocks are described below.

Location. In accordance with recommendation (3), two depots were established in 1981, one at the Société des Gares Frigorifiques et Ports Francs de Genève, Switzerland, and the other in the WHO Regional Office for South-East Asia, New Delhi, India. In the Geneva depot the requisite temperatures were satisfactorily maintained, but in the New Delhi depot the temperatures fluctuated from −10 °C to +10 °C. In 1982, the Smallpox Eradication unit arranged for a refrigeration consultant to visit the Regional Office depot in New Delhi, but it still proved impossible to keep the temperature at the proper level. In addition, the depot was flooded during heavy rains, and all the ampoules of diluent, which were stored separately from the vaccine, were submerged and had to be destroyed. In February 1984 the entire stock of vaccine in the New Delhi depot was transferred to Geneva. It was expected that, because of the high heat stability of freeze-dried smallpox vaccine, the stock would not have been affected by the temperature fluctuations, and, indeed, satisfactory results were obtained when all the batches were tested before their transfer.

The Global Commission's recommendation that vaccine depots should be located in two countries could thus not be implemented. After the difficulties in New Delhi, attempts were made to find a second depot in Japan or the USA, but these failed because the veterinary health authorities of these countries objected to the introduction of calf skin vaccine, which might contain foot-and-mouth disease virus. The Committee on Orthopoxvirus Infections therefore agreed to divide the vaccine stocks equally between the cities of Geneva and Lausanne, which are about 60 kilometres apart and connected by a motorway. Geneva has good communications with the rest of the world, and experience during the smallpox eradication programme showed that, in the event of an emergency, vaccine could be dispatched to any country in the world within 24 hours.

Potency. Although there was good evidence that vaccine could be stored indefinitely at −20 °C, tests carried out in Bilthoven between 1981 and 1983 revealed that the potency of 6 batches of vaccine, from the Islamic Republic of Iran (200 000 doses of vaccine for multiple puncture), and the USA (1.9 million doses of jet injector vaccine), had declined. No attempt was made to determine the causes of this decline; the most probable explanation was that the ampoules were not

WHO / M. VANAPPELGHEM, 1984

Plate 28.2. The reserve of smallpox vaccine in Geneva being checked by J.F. Wickett. At −20 °C it may be expected to retain its potency for many years. Nevertheless, samples are periodically tested, in accordance with a statistically designed procedure.

properly sealed or that the vaccine had too high a moisture content. These batches were removed from the stock and destroyed. Otherwise all samples tested have been found to be of satisfactory potency (Table 28.3).

In 1984, the Committee on Orthopoxvirus Infections discussed the need to keep about 7 million doses of jet injector vaccine donated by Canada, Sweden and the USA. In the Committee's view, bifurcated needles, because of their simplicity, were much to be preferred to jet injectors for the administration of smallpox vaccine should any emergency arise, so that the cost of keeping the jet injector vaccine was not justified. The donor countries were asked whether they would like the batches to be returned to them, but since none was willing to take them, they were destroyed.

Long-term maintenance

During the period 1981–1985 the existence of the WHO vaccine reserve made it much easier for Member States to decide to discontinue both smallpox vaccination and vaccine production. The annual cost of maintaining the vaccine depots amounted to US$21 000 and that of testing to US$3000. Reviewing the situation in March 1986, the Committee on Orthopoxvirus Infections concluded that

Table 28.3. Smallpox vaccine reserve stocks: typical results of initial and subsequent tests of batches provided by manufacturers in 7 countries, 1978–1983[a]

Country of manufacture and batch number	Year					
	1978	1979	1980	1981	1982	1983
Belgium:						
79COI 161		M . .	R 8.6[b]	. .	8.9	. .
German Democratic Republic:						
030 179		M 8.9	R 8.9	. .	8.7	. .
India:						
281 76	MR 8.9	. .	. .	. .	. .	8.7
14 RP 81[c]				M 9.4	. .	9.1
Islamic Republic of Iran:						
46	M . .	R 8.8	. .	. .	. .	8.7
Netherlands:						
72 831	MR . .	. .	8.9	. .	. .	8.8
USSR:						
0386		MR 8.8[b]	. .	. .	. .	8.7
0485			MR 9.1[b]	. .	. .	9.0

[a] Tested by the WHO International Collaborating Centre for Smallpox Vaccine, Bilthoven, except where indicated; titres expressed as $\log_{10}$ pock-forming units per ml of reconstituted vaccine. M = year manufactured; R = year received; . . = data not available. Vaccine was stored at −4 °C before 1980, and at −20 °C thereafter.

[b] Result of test carried out by manufacturer.

[c] Stored initially at the WHO Regional Office for South-East Asia, New Delhi, India.

smallpox vaccine reserves were no longer required and recommended that the maintenance of a global reserve by WHO was no longer indicated. However, it suggested that a decision to offer to return vaccine to donor countries should not be implemented until the situation had been considered by an *ad hoc* committee to be convened by WHO (*Wkly epidem. rec.*, 1986b).

National Stocks of Vaccine

In addition to the WHO reserves, 22 countries reported in 1985 that they had their own national vaccine reserves, which amounted to over 100 million doses, though only about 84 million were properly maintained (Table 28.4). The national health administrations of the countries concerned are responsible for monitoring the potency of these stocks.

Seed Lots of Vaccinia Virus

Seed lots of vaccinia virus produced and kept by the National Institute of Public Health, Bilthoven (see Chapter 11), have been distributed to 3 WHO collaborating centres—namely, the Centers for Disease Control, Atlanta, the National Health Laboratory, Paris, and the National Institute of Health, Tokyo. In addition, in 1985 13 laboratories in countries in which vaccine production had ceased held seed lot material (see Table 28.5), so that, if necessary, production could be rapidly resumed. If there were ever a national emergency, or if the WHO reserve were short of potent vaccine, the seed lots stored in the WHO collaborating centres could be made available to any country that needed to produce vaccine.

Vaccine Production Laboratories

In 1975, towards the end of the Intensified Smallpox Eradication Programme, 84 laboratories were producing freeze-dried or liquid vaccine, the latter being used for routine vaccination programmes in some countries with temperate or cold climates. A few countries discontinued production during the next few years, and, after the declaration of smallpox eradication in 1980, many more did so, often when the national health administrations discontinued routine smallpox vaccination programmes (Table 28.5).

In 1985, only 14 laboratories in 11 countries were still producing vaccine, mainly for the use of national defence forces or to stock national emergency reserves.

INVESTIGATION OF SUSPECTED SMALLPOX CASES

"Experience in many countries indicates that reports of suspected cases of smallpox can be expected to be received from many sources for several years after the certification of global eradication. The importance of thorough investigation of these reports, if necessary with laboratory testing, is illustrated by the fact that one such report led to the recognition of human monkeypox. It is also important that public confidence in the fact of eradication should be maintained by thorough and prompt investigation of all reports and disclosure of the results to health officials throughout the world.

Table 28.4. Known national stocks of smallpox vaccine, by WHO region, 1985[a]

WHO region	Number of countries	Number of doses[b]	
		Held	Properly maintained[c]
Africa	1	30 000 000	30 000 000
Americas	4	23 934 720	23 659 070
South-East Asia	2	13 976 100	..
Europe	9	19 145 500	17 845 500
Eastern Mediterranean	2	3 013 500	..
Western Pacific	4	12 395 500	12 395 500
Total	22	102 465 320	83 900 070

[a] Minimum figures; 3 of the 22 countries holding vaccine reserves did not indicate the number of doses held and are excluded from the totals shown.
[b] Of 0.1 ml, as used for multiple puncture vaccination.
[c] Held at a temperature of 4 °C or lower and periodically tested for potency; .. = data not available.

Table 28.5. Countries producing smallpox vaccine, 1977–1985, and countries holding seed lots, 1985, by WHO region

WHO region	Countries producing vaccine									Countries holding seed lots[a]
	1977	1978	1979	1980	1981	1982	1983	1984	1985	
Africa	5	5	3	1	0	0	0	0	0	1
Americas	14	14	10	3	1	1	1	1	1	3
South-East Asia	7	6	6	2	1	1	0	0	0	3
Europe	25	23	21	13	13	10	8	8	8	1
Eastern Mediterranean	7	7	6	2	2	1	1	0	0	2
Western Pacific	18	18	16	5	5	2	2	2	2	3
Total	76	73	62	26	22	15	12	11	11	13

[a] Excluding those still producing vaccine.

"Suspected smallpox cases should therefore be investigated by experienced personnel. WHO should provide an effective system to promote, coordinate, and participate in the investigation of suspected smallpox cases. The international smallpox rumour register that was established by WHO in Geneva in January 1978 should be maintained.

"The reward of US$1000 established by the Director-General in 1978 in accordance with resolution WHA31.54 should be discontinued, since global eradication has now been certified.

"*Recommendation (7).* In order to maintain public confidence in the fact of global eradication, it is important that rumours of suspected smallpox, which can be expected to occur in many countries, should be thoroughly investigated. Information should be provided to WHO, if requested, so that it can be made available to the world community.

"*Recommendation (8).* WHO should maintain an effective system to coordinate and participate in the investigation of suspected smallpox cases throughout the world. The international smallpox rumour register should be maintained."

Guidelines for the Management of Suspected Cases of Smallpox

Early in 1981, WHO distributed to all national health administrations a document entitled *Management of suspected cases of smallpox in the post-eradication period* (WHO/SE/80.157 Rev. 1), which provides a practical guide on how to act if a report of a suspected case of smallpox is received. One of the most important pieces of advice given is that vaccination should not be carried out unless a presumptive diagnosis of smallpox has been established, based on an examination by a physician with extensive experience in the clinical diagnosis of the disease and on a laboratory report that poxvirus particles have been demonstrated by electron microscopy. This advice was included because, when the document was being prepared, certain health officials who were not convinced that eradication had been achieved had recommended that vaccination programmes should be undertaken if a suspected case of smallpox were to be reported.

The International Rumour Register

In accordance with recommendations (7) and (8), post-smallpox-eradication surveillance was initiated by the Smallpox Eradication unit in 1980 and is being continued; 131 rumours reported to WHO between January 1980 and December 1986 were investigated with the results shown in Table 28.6. In fact, only a minority of rumours come to the attention of WHO Headquarters, the majority being dealt with at country level without being referred to WHO. In India, for example, about 2000 rumours were investigated and 79 specimens examined virologically between 1980 and 1984.

The main sources of rumours reaching WHO Headquarters have been the general public, tourists, physicians and the mass media. On receiving information of a rumour, WHO Headquarters usually contacts the WHO regional office concerned and requests that an investigation should be undertaken. If the situation is considered to be urgent, WHO Headquarters contacts the informant direct, asking for more details; at the same time it requests the government health services, as well as WHO epidemiologists in the country

or at the regional office concerned, to investigate the rumour. The results of investigations of rumours deemed to be important because of the wide publicity they have received, or for other reasons, are published promptly in the *Weekly epidemiological record*, so that Member States are kept informed.

All these rumours have turned out to be false alarms, thus confirming that there has been no evidence of smallpox anywhere in the world since the declaration by WHO of smallpox eradication in 1980.

In checking rumours reported to WHO, use is made of the diagnostic services provided by the WHO collaborating centres at the Centers for Disease Control, Atlanta, USA, and the Moscow Research Institute for Viral Preparations, Moscow, USSR. All investigations, both by the WHO collaborating centres and by national laboratories, have failed to reveal variola virus in any sample tested.

Nature and sources of rumours reported

As was mentioned above, 131 rumours were reported to WHO Headquarters between January 1980 and December 1986 (Table 28.6). About half the total number of these reports were received between 1980 and 1982; by 1985–1986, only 10 were being reported annually. Experience in India, where most rumours were investigated locally without being referred to WHO, was comparable, the yearly totals of specimens investigated by the smallpox reference laboratory of the National Institute of Communicable Diseases being 30, 16, 8, 10 and 15, respectively, over the period 1980–1984.

Of the 131 rumours reported to Headquarters, about 70% were investigated and the results made known to WHO within 2 months, but delays of up to 6–9 months occurred in some cases. The principal diseases misdiagnosed as smallpox were chickenpox and measles, which had also been the main causes of misdiagnosis before smallpox was eradicated (see Chapter 1). A significant proportion of the rumours arose from inaccurate reporting or recording. Even cholera was sometimes reported as smallpox in the mass media. Human monkeypox was occasionally misdiagnosed as smallpox and reported as such, but these cases have been excluded from the register since they occurred in Zaire, in which the disease has been under special surveillance since 1982 (see below).

Examples of the kinds of rumours reported

Rumours arose from various sources and a wide variety of actions were taken to investigate them. A few examples are given below; others have been described by Khodakevich & Arita (1985).

Rumours circulated by the mass media. The national and international news media were a common source of rumours and occasionally reported outbreaks of smallpox in areas in which epidemics of an infectious disease had occurred and caused several deaths. Expecting to find an increased incidence of infectious diseases in refugee camps and regions affected by famine, reporters sometimes alleged the occurrence of smallpox despite the lack of any supporting evidence. For example, *Newsweek*, on 26 November 1984, carried an article describing the famine situation in Ethiopia, in which it stated: "... Starvation brought other ailments with it, including influenza, measles, tuberculosis, diarrhea, smallpox, ty-

Table 28.6. International rumour register: suspected cases of smallpox reported to WHO Headquarters, Geneva, by WHO region, 1980–1986

WHO region	Number of reports								Results of investigation			
	1980	1981	1982	1983	1984	1985	1986	Total	Chicken-pox	Measles	Skin disease	Erroneous reports by news media
Africa	9	11	5	5	6	5	6	47	18	7	8	14
Americas	3	6	0	4	5	0	1	19	11	1	3	4
South-East Asia	12	4	3	8	8	5	2	42	17	7	2	16
Europe	1	2	0	0	0	0	0	3	3	0	0	0
Eastern Mediterranean	4	3	2	1	2	0	0	12	2	1	2	7
Western Pacific	2	4	0	1	0	0	1	8	3	3	1	1
Total	31	30	10	19	21	10	10	131	54	19	16	42

phus and kwashiorkor . . .". When WHO drew the attention of the editor of the magazine and of health staff in Ethiopia to the erroneous nature of this report, it transpired that there had been cases of measles, but not of smallpox.

Rumours related to variolation. On 18 November 1983, WHO was informed by the Kenyan health services that a suspected case of smallpox had occurred in Kenya in an adult male from Nandi Hill Estate in the Rift Valley Province. The patient was hospitalized on 8 November and died on 15 November, 3 days after developing a papular rash, mainly on the face and limbs. Scab specimens were taken and sent immediately from Nairobi to the WHO collaborating centre at the Centers for Disease Control, Atlanta.

It was noted that the patient, whose vaccination status was not known, had been a traditional healer, perhaps a former variolator who might have inoculated himself with old material still in his possession, but that his 5-year-old son had had chickenpox shortly before the onset of the illness. On 21 December, the collaborating centre in Atlanta informed WHO that herpesvirus particles had been seen in the specimens by electron microscopy, and this information was immediately relayed to the Kenyan health authorities. Virus cultivation on the chorioallantoic membrane gave negative results for smallpox. The prompt reporting and collection of specimens by the Kenyan health services, and the equally prompt laboratory investigation by the WHO collaborating centre, led to the correct diagnosis of this case within a few days of its occurrence.

Scabs on old corpses. Early in 1985 some student archaeologists were engaged in excavating the vaults of a church near Spitalfields, London. One coffin was found to contain the well-preserved remains of a person who had died of smallpox in about 1840. As a precaution, the United Kingdom Health and Safety Executive closed the site and vaccinated the 3 student archaeologists concerned, and "scab" material from the corpse was sent to the WHO collaborating centre in Atlanta. Exhaustive electron microscopic examination there revealed one object that might have been a poxvirus particle but all attempts at cultivation were unsuccessful. Later, Fornaciari & Marchetti (1986) published photographs of objects that they considered to be poxvirus particles on the basis of electron microscopy of material taken from a vesiculopustular eruption on the mummy of a 2-year-old boy who died in Naples in the 16th century. Exhaustive testing in the WHO collaborating centres failed to reveal any infectious virus in samples of this material. Bodies buried in Artic permafrost, referred to in Chapter 30, might pose a greater risk, although very few smallpox victims would have been interred in such places.

Efficacy of the international rumour register

The international rumour register constituted the ultimate level of reference in a system operating primarily at the country or WHO regional office level for the investigation of rumours of smallpox, although it often received rumours direct from a source rather than through the network. This continuing surveillance failed to find any evidence of the recurrence of smallpox anywhere in the world. Had there not been such surveillance by WHO, backed up by special investigations at the WHO collaborating centres, it is highly likely that some rumours would have had significant repercussions, resulting in damage to public confidence in the WHO declaration, and even the initiation of a mass vaccination programme against smallpox. In the event, vaccination was never needed nor was it ever recommended, since no case occurred which satisfied the requirements laid down by the guide to the management of suspected cases of smallpox. The confidence thus built up undoubtedly assisted in ensuring the universal discontinuation of routine smallpox vaccination.

LABORATORIES RETAINING VARIOLA VIRUS STOCKS

"A committee of experts meeting in February 1979 advised the Global Commission that it was necessary for scientific reasons to preserve stocks of variola virus in a few laboratories, but that the position should be reviewed in 1982. In view of the potential danger of reintroduction of smallpox from variola virus stocks held in laboratories, no more than four WHO collaborating centres should be approved as suitable for the storage of and work with variola virus in accordance with WHO safety standards. These WHO collaborating centres should report annually to WHO and their containment facilities should be periodically inspected to ensure that storage is secure and that safe operating conditions are maintained. All other laboratories

should be asked to destroy any stocks of variola virus that they hold, or to transfer them to an approved WHO collaborating centre.

"*Recommendation (9).* No more than four WHO collaborating centres should be approved as suitable to hold and handle stocks of variola virus. A collaborating centre would be approved only if it had adequate containment facilities. Each such centre should report relevant information on its safety measures annually to WHO and be inspected periodically by WHO.

"*Recommendation (10).* Other laboratories should be asked to destroy any stocks of variola virus that they hold, or transfer them to an approved WHO collaborating centre."

Reduction in Number

As early as 1976 the Smallpox Eradication unit began trying to reduce the number of laboratories holding stocks of variola virus (see Chapter 30). This was successful in that the number of such laboratories fell from 75 in 1975 to 7 at the time of the final meeting of the Global Commission in December 1979 (see Chapter 30, Tables 30.6 and 30.7).

A laboratory-associated outbreak of smallpox in Birmingham, England, in 1978 and the declaration of smallpox eradication by the Thirty-third World Health Assembly in 1980 provided a strong incentive for laboratories not actively working with variola virus to destroy their stocks or transfer them to one of the WHO collaborating centres that was equipped with a high-security containment laboratory. By the end of 1981, only 4 laboratories still retained variola virus stocks: one each in South Africa, the United Kingdom, the USSR and the USA. Except for the South African laboratory, all were WHO collaborating centres for the diagnosis of, or research on, orthopoxvirus infections.

Between 1979 and 1982 Dr Keith Dumbell, a member of the Committee on Orthopoxvirus Infections, was engaged in research on variola virus, including the cloning of its DNA, in the biocontainment laboratory at the Centre for Applied Microbiology and Research, Porton Down, England. With the completion of this work in September 1982, all the variola virus stocks held at Porton Down were transferred to the Centers for Disease Control, Atlanta.

BY COURTESY OF J. SPAANDER

Plate 28.3. The first stage in the transfer of stocks of variola virus from the National Institute of Public Health, Bilthoven, Netherlands, to the Centers for Disease Control, Atlanta, GA, USA, on 2 December 1981, with appropriate safeguards.

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Smallpox virus destroyed

VARIOLA, that is smallpox isolates contained in 177 vials were destroyed at the P4 high security laboratory at the South African National Institute for Virology in Johannesburg on 9 December 1983.

Previously the deadly virus had been stored in three centres, i.e. the Centre for Disease Control in Atlanta, USA, the Russian Institute for Virus Production in the USSR, and the SA National Institute for Virology. The South African laboratory had been approved and regularly inspected by the World Health Organisation, the last inspection having been in February 1983.

Because research regarding the genotype mapping of the smallpox virus had been completed and it was no longer required for the preparation of vaccine or other research, there was no reason for keeping the virus here any longer.

Normally the virus had been stored at 20°C and in order to destroy all the isolates the vials were placed in an autoclave and submitted to 130°C and 240 kpa for 20 minutes. Copies of all the isolates are, however, still available at the Centre for Disease Control in Atlanta.

The last known natural case of smallpox occurred in October 1977 in Somalia, and in 1980 the WHO declared the world free of the dreaded disease.

Dr The Honourable C V van der Merwe, Minister of Health and Welfare officiated and pressed the button to set the destruction process in motion. It was also done in the presence of Prof Keith Dumbell, an observer and former member of the World Health Organisation Committee on the Global Eradication of Smallpox.

Prof Keith Dumbell, (left) former member of the World Health Organisation Committee on the Global Eradication of Smallpox was present to witness the destruction of all the virus. With him is Dr Bob Swanepoel, Senior Virologist in charge of the P4 Laboratory.

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Plate 28.4. Destruction of variola virus stocks at the National Institute for Virology, Sandringham, South Africa, on 9 December 1983. The operation was carried out by the Minister of Health and Welfare of South Africa and witnessed by Dr K.R. Dumbell (left), a member of the Committee on Orthopoxvirus Infections and Dr Bob Swanepoel (right), Senior Virologist in charge of the P4 Laboratory.

In South Africa, the National Institute for Virology in Sandringham retained locally isolated strains of variola virus in a high-security biocontainment laboratory, although they had not been used for many years. Because of South Africa's political isolation, the health authorities were afraid that, if the virus were destroyed, they would have difficulties in diagnosing variola virus should any unexpected circumstances occur. However, when cloned preparations of fragments of variola virus DNA (which cannot replicate and are completely safe to work with) were made available to the National Institute for Virology by Dr Dumbell, their anxieties were relieved and the South African government destroyed all virus stocks in December 1983, in the presence of Dr Dumbell (Plate 28.4).

Since the beginning of 1984, stocks of variola virus have been retained only in the WHO collaborating centres in the Centers for Disease Control, Atlanta, USA, and the Moscow Research Institute for Viral Preparations, USSR, each of which possesses a high-security biocontainment laboratory. During 1983, the remodelling of these laboratories was completed, and both were approved by WHO inspection teams for work with variola virus. The retention of these facilities and their associated personnel has been costly, but the governments of the USSR and the USA have continued to provide the necessary support because of their value in examining material from cases of human monkeypox and from suspected cases of smallpox referred to them through the international rumour register.

The stocks held at the Centers for Disease Control include those transferred from the National Institute of Health, Japan; the National Institute of Public Health, Netherlands; the Centre for Applied Microbiology and Research, United Kingdom; the American Type Culture Collection, New York; and the United States Army Medical Research Institute for Infectious Diseases, Frederick, Maryland, USA. In addition to variola virus stocks, the Moscow laboratory holds "white-pox" viruses isolated from animal specimens and from monkeypox virus stocks (see Chapter 30). These virus stocks are regarded as just as dangerous as variola virus and are kept in the containment laboratory under the same security conditions as that virus. The variola virus stocks in Atlanta and Moscow contain strains of variola major and variola minor viruses from most areas in which smallpox has occurred since 1967.

In March 1986 the Committee on Orthopoxvirus Infections reviewed its policy on the retention of stocks of variola virus in the light of the existence of DNA from 5 strains of variola virus cloned in *Escherichia coli* and the current situation in relation to the use of the virus in research and diagnosis. The meeting was attended by senior public health officials from the two countries in which variola virus stocks are currently held—namely, the USSR and the USA. The Committee advised WHO that the cloned DNA would be satisfactory both for assisting diagnosis in any situation in which that might prove necessary and for archival purposes. Since the Committee considered that research work requiring the use of viable variola virus was no longer justified, it recommended that remaining stocks of the virus should be destroyed, and that this recommendation should be widely publicized but not implemented until approval had been

Table 28.7. Inspections of laboratories holding stocks of variola virus, 1978–1986

Laboratory	Year								
	1978	1979	1980	1981	1982	1983	1984	1985	1986
China:									
National Institute for the Control of Pharmaceutical and Biological Products, Beijing	..	+[a]							
Netherlands:									
National Institute of Public Health, Bilthoven	..	+[b]							
South Africa:									
National Institute for Virology, Sandringham	+	+	..	+	..	+[c]			
USSR:									
Moscow Research Institute for Viral Preparations, Moscow	..	+	+	..	..	+	..	..	+
United Kingdom:									
St Mary's Hospital Medical School, London	+[d]								
Centre for Applied Microbiology and Research, Porton Down, Wilts.	..	..	+	+[e]					
Department of Medical Microbiology, University of Birmingham	+[f]								
USA:									
Centers for Disease Control, Atlanta, GA	..	+	..	+	+	..	+	+	..
United States Army Medical Research Institute for Infectious Diseases, Frederick, MD	..	+[g]							

[a] Stocks destroyed in 1983.
[b] Stocks transferred to Centers for Disease Control in December 1981.
[c] Stocks destroyed in 1983.
[d] Stocks transferred to Centre for Applied Microbiology and Research in September 1978.
[e] Stocks transferred to Centers for Disease Control in September 1982
[f] Stocks destroyed in September 1978.
[g] Stocks transferred to Centers for Disease Control in April 1980.

given by an *ad hoc* committee of experts, which it suggested should be convened by WHO (*Wkly epidem. rec.*, 1986b).

Inspection

Since 1978, WHO inspection teams consisting of epidemiologists, virologists and biosafety experts have periodically visited all the laboratories retaining variola virus, in order to determine whether each of them satisfied the relevant WHO requirements. Inspections have been made annually or every second or third year (Table 28.7), a special check-list being used to cover all safety aspects. These inspections have revealed that problems sometimes occur in the efficient operation of biocontainment laboratories, even though the personnel concerned are highly trained.

HUMAN MONKEYPOX

"Human monkeypox is a rare zoonosis that was not recognized until smallpox was eliminated from the area where it occurs. Clinically it resembles smallpox. Human cases can be expected to appear where the ecological conditions are appropriate and perhaps to show some increase as smallpox vaccination ceases and immunity wanes. Because it is caused by a poxvirus distinct from variola virus and has a limited capacity to spread between humans, monkeypox virus does not constitute a threat to the permanence of smallpox eradication. However, it is important that close surveillance of human cases should continue and that further investigation should be made into the natural history of the disease.

"*Recommendation (11).* In collaboration with country health services, WHO should organize and assist a special surveillance programme on human monkeypox, its epidemiology, and its ecology in areas where it is known to have occurred. The programme should continue until 1985, when a further assessment of the situation should be made".

The demonstration that monkeypox virus caused sporadic infections in man was an important scientific discovery directly attributable to the smallpox eradication programme. Consideration of the ecology of the disease indicated that it was not a new, but a newly discovered, one. The implementation of recommendation (11) of the Global Commission constituted the greater part of the post-smallpox-eradication programme. The organization of surveillance is described below and the results of these studies are reported in Chapter 29. Activities relating to human monkeypox were planned by Arita and Ježek, and implemented by the joint efforts of WHO, national staff in western Africa and Zaire, and the WHO collaborating centres.

Epidemiological Surveillance in Zaire

Work in Zaire from 1980 onwards built on the surveillance system established there in the late 1970s (see Chapter 29).

Seminar in Brazzaville, May 1980

A seminar on the surveillance of monkeypox and viral haemorrhagic fevers was held in the WHO Regional Office for Africa, Brazzaville, Congo, in May 1980. Its objective was to devise ways of further strengthening the surveillance of monkeypox and viral haemorrhagic fevers in areas of central and western Africa in which these zoonoses occurred. WHO staff from Geneva and the regional office and delegates from 10 countries in central and western Africa and 2 countries in eastern and southern Africa participated in the seminar, which recommended that the health services of each country should develop special surveillance of these diseases. A document entitled *Procedures for the surveillance and management of monkeypox and viral haemorrhagic fevers* (CDS/80.1) was promptly prepared by WHO and widely distributed, but only 3 cases of monkeypox were reported in 1980 and 8 in 1981.

Health-institution-based surveillance in Zaire

In the summer of 1980, Arita visited Kinshasa, Zaire, to discuss with the health authorities and the staff of the monkeypox programme how to strengthen surveillance activities. A review of the previous 3 years of surveillance in Zaire revealed 2 important findings: (1) most of the cases reported were patients who had visited hospitals or dispensaries seeking medical treatment; and (2) an earlier recommendation that mobile surveillance teams should visit all health stations every 3 months had never been implemented because of limited resources. Furthermore,

African Viral Haemorrhagic Fevers

In addition to smallpox and yellow fever, which were for centuries the commonest viral diseases with haemorrhagic manifestations, several other viral haemorrhagic fevers have been recognized in recent decades (McCormick & Johnson, 1984). All are presumed to be contracted by man from an animal source. Three of them, Ebola virus disease, Lassa fever and Crimean-Congo haemorrhagic fever, occur in central and western Africa. The natural history of Ebola virus, which caused a major outbreak in a hospital in Zaire in 1976, is unknown, and there are many gaps in our knowledge of the ecology of the other two diseases. In the studies planned in Zaire, surveillance for haemorrhagic fever was added to monkeypox surveillance, since the geographical areas in which these diseases have been identified overlap and the methods of investigation are similar. In this way the best use could be made of the sparse resources available in central and western Africa.

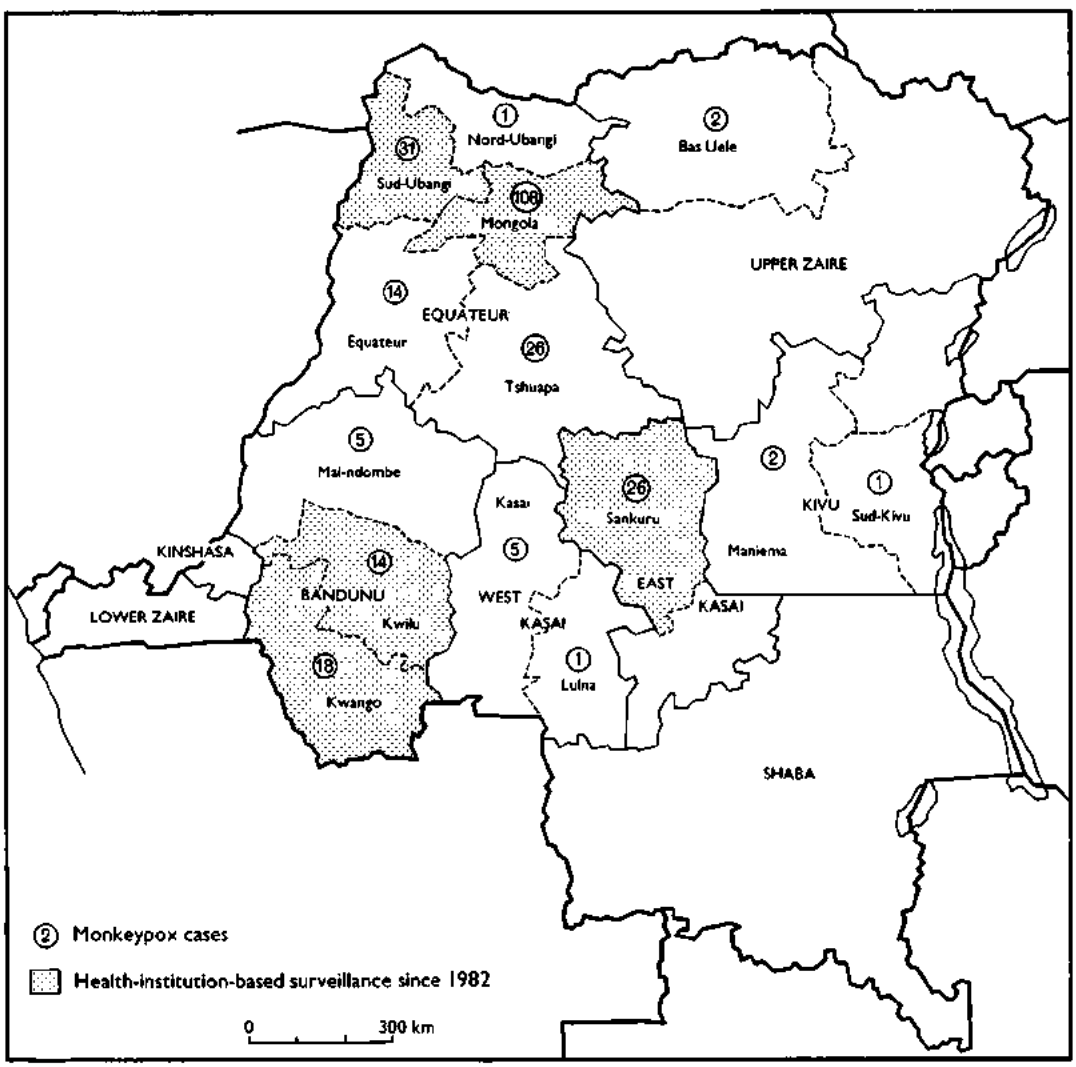


Fig. 28.1. Zaire: subregions where intensive health-institution-based surveillance has been carried out since 1982, and numbers of cases of human monkeypox by subregion, 1970 – 1984.

Health-Institution-Based Surveillance

The idea of using health-institution-based surveillance for human monkeypox in Zaire stemmed from experience in western Africa with Lassa fever. This is a haemorrhagic fever caused by an arenavirus, which was first recognized in a hospital outbreak in Lassa, Nigeria, in January 1969. Outbreaks subsequently occurred in hospitals in several other parts of western Africa, and in the early 1970s it was thought to be a rare zoonosis, which was associated with a case-fatality rate of about 50% when outbreaks did occur. In 1977 a study was commenced in the Kenema District, Sierra Leone, under the direction of Dr Joseph B. McCormick, of the United States Center for Disease Control, to assess the prevalence and importance of Lassa fever. A surveillance system based on the hospital reporting of febrile disease was established, together with a small diagnostic laboratory. Local personnel were trained to take specimens from patients and to investigate any suspected cases of Lassa fever. The system was successful and showed that the disease was a common cause of hospital admission for both adults and children, with several hundred cases occurring annually in the area. The severity of cases varied greatly, with a case-fatality rate of less than 5% among subjects sick enough to report to hospital. The overall case-fatality rate was even lower, since other studies revealed that 6% of a population surveyed in Kenema District had complement-fixing antibodies against Lassa virus while only 0.2% had recognized disease (Fraser et al., 1974).

This experience suggested that health-institution-based surveillance might be a practical method for monitoring the prevalence of a disease in areas in which the infrastructure for public health and preventive medicine was rudimentary.

the mobile teams were frequently used in the control of cholera outbreaks. In the circumstances, health-institution-based surveillance, which was based on the collaboration of hospital and dispensary staff, appeared to be the most promising method of obtaining more information about human monkeypox. The system was concentrated in 4 subregions of 3 regions in northern Zaire, which had extensive areas of tropical rain forest and in which a relatively high incidence of the disease had been observed in 1978 and 1979.

Between December 1980 and November 1981, 4 seminars on monkeypox and viral haemorrhagic fever surveillance were organized by Ježek, in collaboration with Dr Kalisa Ruti, of the Ministry of Health of Zaire, in which medical staff from 154 health institutions participated. The seminars, which brought together all senior staff of health units working within a radius of 250–500 kilometres, were held in Lisala for Mongola subregion (December 1980), in Gemena for Sud-Ubangi subregion (February 1981), in Lodja for Sankuru subregion (June 1981) and in Kikwit for Kwango and Kwilu subregions (November 1981) (see Fig. 28.1). It was the first time in central and western Africa that seminars had been devoted specifically to these newly discovered diseases, with the participation of senior government officials and technical experts. Monkeypox recognition cards, sample collection kits and the document *Instructions for health-institution-based surveillance of monkeypox and viral haemorrhagic fevers* (CDS/80.2) were distributed to participants. It was announced that a reward of 500 zaires (US$90) was to be offered to any person, including health staff, who reported a case of human monkeypox.

Following each seminar, health-institution-based surveillance for human monkeypox and viral haemorrhagic fevers, supported by WHO funds, was developed in each subregion (Fig. 28.1), and by the end of 1981 was functioning effectively in all of them. The selected areas together represented about 15% of the land area of Zaire and contained about 5 million inhabitants—18% of the country's population—among whom 89% of the human monkeypox cases recorded in Zaire up to that time had been detected. Sporadic cases of Ebola haemorrhagic fever were also known to occur in some of the

selected areas. A total of 154 health establishments participated in surveillance activities, including 55 government and missionary hospitals, 62 dispensaries and 37 other health units (health centres and maternal and child health clinics). They were responsible for the discovery, identification and notification of suspected cases of monkeypox or viral haemorrhagic fever as well as the proper collection and dispatch of specimens for laboratory investigation. Their activities were supported by 4 mobile surveillance teams, which provided technical advice and material support. This well-designed and well-supervised surveillance system based on peripheral health units and mobile surveillance teams was supplemented by posting special surveillance officers in 4 areas of epidemiological priority to carry out village-based surveillance and assist in ecological surveys.

The striking increase in the number of monkeypox cases reported in Zaire in 1982 (39 cases) and 1983 (84 cases), as compared with previous years (see Chapter 29, Table 29.3), was due principally to the strengthened health-institution-based surveillance and intensified field activities, since 90% of the cases reported in Zaire in 1982–1983 were detected in areas of strengthened surveillance; and health-institution-based surveillance itself accounted for about 60% of the reported cases. The description of the clinical features and epidemiology of human monkeypox given in Chapter 29 is based on the results obtained by this intensive surveillance in Zaire, supported by laboratory studies in the WHO collaborating centres in Atlanta and Moscow.

Serological survey of unvaccinated subjects

In order to estimate the prevalence of human monkeypox in central and western Africa, serological surveys were conducted on unvaccinated subjects living in tropical rain forest areas of the Congo, Côte d'Ivoire, Sierra Leone and Zaire (see Chapter 29, Table 29.10). These surveys revealed that at least 0.7% of the persons concerned, who lived in areas in which monkeypox could be expected to occur, had specific antibody to it. Follow-up examinations of persons with positive serological findings indicated that over half of them had no history of a vesiculopustular disease or any facial pockmarks. It was concluded that at least some of them had suffered from a subclinical infection with monkeypox virus (see Chapter 29).

Studies on the ecology of monkeypox virus

In 1984–1986, Dr Lev Khodakevich and his collaborators carried out surveys in the Central African Republic and Zaire in order to try to determine the reservoir host of monkeypox virus. These were successful in incriminating squirrels as a significant wild animal host of monkeypox virus in some areas (see Chapter 29).

Review of Monkeypox, March 1986

In its review of the situation in March 1986, the Committee on Orthopoxvirus Infections noted that excellent progress had been made in understanding the epidemiology of human monkeypox and the ecology of monkeypox virus since its third meeting, in 1984. The results of these studies, described in detail in Chapter 29, indicated that human monkeypox was a rare zoonosis in which human-to-human infection sometimes occurred. The Committee concluded that it was now clear that the disease was not a serious public health problem and recommended that WHO involvement in monkeypox surveillance and research should be phased out (*Wkly epidem. rec.*, 1986b).

LABORATORY INVESTIGATIONS

"There are still some important unsolved virological problems that are relevant to smallpox eradication, especially in relation to the "whitepox" viruses. The solution of these problems and preparedness for unexpected problems that might arise in relation to smallpox or other poxvirus diseases of man call for the maintenance of suitable virological expertise.

"Besides encouraging scientists in various nations to continue research on orthopoxviruses, WHO has responsibility for the regular testing of the potency of the WHO vaccine reserves and for the provision of laboratory diagnostic facilities for suspected smallpox cases. It can best discharge this responsibility by continuing the system of WHO collaborating centres. If competent research workers from laboratories not approved by WHO for work with variola and whitepox viruses wish to conduct experiments with these viruses, facilities should, if possible, be provided by a suitable WHO

collaborating centre. These experiments must be approved by the appropriate WHO committee.

"*Recommendation* (*12*). WHO should continue to encourage and coordinate research on orthopoxviruses.

"*Recommendation* (*13*). WHO should maintain the system of WHO collaborating centres for carrying out diagnostic work and research on orthopoxviruses.

"*Recommendation* (*14*). Research workers who do not work in a WHO collaborating centre and who wish to carry out experiments with variola or whitepox virus that are approved by the appropriate WHO committee should be offered the use of the special facilities in a WHO collaborating centre.

"*Recommendation* (*15*). Research on poxviruses other than variola or whitepox viruses should not be performed under circumstances where there is any possibility of cross-contamination with these two agents."

Laboratory Diagnosis of Suspected Smallpox and Monkeypox

Since 1980 the two WHO collaborating centres in Atlanta (Dr James Nakano, director) and Moscow (Dr Svetlana Marennikova, director) have continued the diagnostic testing of specimens collected from suspected cases of smallpox throughout the world, employing for this purpose laboratory workers with extensive experience obtained during the Intensified Smallpox Eradication Programme. In addition to examining material from some of the cases reported to the international rumour register, the centres examined specimens collected from suspected cases of human monkeypox and from other poxvirus infections (tanapox and molluscum contagiosum) in western and central Africa. Between 1980 and 1984, 16 650 specimens were tested (Table 28.8), the majority having been collected during serological surveys for human monkeypox. Requests for viral isolation came mainly from countries in which human monkeypox cases had occurred or were suspected, mostly as part of the special surveillance for human monkeypox described earlier in this chapter and in greater detail in Chapter 29. In addition, 193 requests were received from 28 other countries in connection with suspected cases of smallpox. In no case was variola virus found.

Table 28.8. Numbers of specimens (lesion material and sera) examined for evidence of orthopoxvirus infection by the WHO collaborating centres in Atlanta and Moscow, by WHO region, 1980–1984

WHO region	1980		1981		1982		1983		1984		Total	
	Countries	Specimens	Countries	Specimens	Countries	Specimens	Countries	Specimens	Countries	Specimens	Countries	Specimens
Africa[a]	2	1 970	4	10 332[b]	2	477	4	1 211	2	939	6	14 929
Africa[c]	9	53	5	1 539[d]	1	3	2	3	2	3	14	1 601
Americas	0	0	1	16	0	0	1	10	0	0	2	26
South-East Asia	1	1	0	0	1	13	2	3	0	0	3	17
Europe	1	1	0	0	0	0	0	0	0	0	1	1
Eastern Mediterranean	6	18	4	44	3	9	1	4	0	0	8	75
Western Pacific	1	1	0	0	0	0	0	0	0	0	1	1
Total	20	2 044	14	11 931	7	502	10	1 231	4	942	35	16 650

[a] Countries in which monkeypox has been found (Cameroon, Central African Republic, Côte d'Ivoire, Nigeria, Sierra Leone, Zaire).
[b] Includes 8867 specimens of serum from Côte d'Ivoire, Sierra Leone and Zaire collected in serological surveys (see Chapter 29, Table 29.10).
[c] Other countries (i.e., those not mentioned in footnote[a]).
[d] Includes 1433 specimens of serum from the Congo collected in serological surveys (see Chapter 29, Table 29.10).

Continuing Research on Orthopoxviruses

Research problems of importance to WHO in the post-smallpox-eradication era fell into 3 categories: (1) analysis of the DNA of variola virus and other orthopoxviruses; (2) development of sensitive tests to detect antibody specific to monkeypox virus in human and animal sera; and (3) ecological and epidemiological research on the natural history of monkeypox.

Analysis of orthopoxvirus DNA

In June 1979, in view of the fact that the certification of global eradication was imminent, WHO organized a meeting on orthopoxvirus research, which was co-sponsored by the Centers for Disease Control and held in Atlanta (SME/79.9). The objective was to define fields of research relevant to the post-smallpox-eradication era. At that time there was still considerable controversy as to the significance of the "whitepox" viruses that had been isolated in laboratories in the Netherlands (Bilthoven), and the USSR (Moscow). Following discussions at the meeting, collaborative work with personnel from the Bilthoven and Moscow laboratories was carried out by Dr Dumbell at the Centre for Applied Microbiology and Research, Porton Down, and by Dr Joseph Esposito at the Centers for Disease Control. These studies showed that all strains of "whitepox" virus were identical with variola virus and probably originated as laboratory contaminants (see Chapter 30).

Dr Dumbell, Dr Esposito and their colleagues continued to carry out studies on the DNA of various strains of variola and monkeypox viruses, thereby considerably increasing our understanding of these viruses; the results of these studies are summarized in Chapters 2, 29 and 30. Dr Esposito also produced, for the first time, restriction endonuclease maps of the DNA of camelpox, taterapox and raccoonpox viruses, all of which are species of *Orthopoxvirus* (Esposito & Knight, 1985).

Both Dr Dumbell and Dr Esposito cloned variola virus DNA in *Escherichia coli*, rendering it safe to handle in any laboratory. By March 1986, libraries of cloned fragments of the DNA of 2 strains of variola major virus (Harvey and a strain from Bangladesh) and of 3 strains of variola minor virus (2 strains of alastrim virus and a strain from Somalia) were available. At that time, the Committee on Orthopoxvirus Infections suggested that a western African strain should also be cloned, so as to provide a reasonable range of strains of variola virus DNA for archival purposes and for scientific research. It was because this material was or would be available that the Committee recommended the destruction of the remaining stocks of viable variola virus (see below).

Development of tests for antibody specific to monkeypox virus

The genus *Orthopoxvirus* includes 9 known species, of which 3 (vaccinia, monkeypox and taterapox viruses) or possibly 4 (with Uasin Gishu disease virus, an orthopoxvirus that affects horses in Kenya) occur in western and central Africa. All species of *Orthopoxvirus* show extensive serological cross-reactivity. Methods existed for making presumptive species-specific diagnoses of infections with monkeypox, variola and vaccinia viruses by tests on sera absorbed with viral suspensions, but their use with sera from healthy animals or man taken during ecological or epidemiological surveys gave uncertain results. It was therefore difficult to evaluate the significance of the large number of orthopoxvirus-positive sera obtained in ecological surveys in Zaire in 1979 and earlier (see Chapter 29). Consequently, there was an urgent need for a sensitive test for monkeypox-specific antibodies which could be used with sera collected during ecological and epidemiological surveys to support surveillance and field studies of human monkeypox. Such a test would also help to determine the extent of subclinical and person-to-person infection with monkeypox virus.

Several steps were taken to try to solve this problem. In 1981 Dr W. K. Joklik, of Duke University Medical Center, Durham, North Carolina, USA, attempted to develop a radioimmunoprecipitation test for the identification of monkeypox-specific antibody, but without success. Monoclonal antibodies that reacted with monkeypox virus but not with certain other orthopoxviruses were developed by Dr Y. Ichihashi in Dr Joklik's laboratory, and at the WHO collaborating centre in Atlanta, in 1983. Subsequently Dr Ichihashi continued work on monoclonal antibodies at Niigata University, Japan, with financial assistance from WHO; he developed a number of monkeypox-specific and vaccinia-

specific monoclonal antibodies and an antigen-binding inhibition test that could be used with certain sera to detect monkeypox-specific antibodies. However, at the time of writing this test requires further development.

Fortunately, in 1985 Dr Nakano developed modifications of the radioimmunoassay adsorption test which made it possible to evaluate the significance of some of the orthopoxvirus antibody-positive animal sera collected in Zaire in 1979 (see Chapter 29).

Other Studies of Variola and "Whitepox" Viruses

Recommendation (14) envisaged the possibility that workers in laboratories other than the two WHO collaborating centres might wish to work with variola or "whitepox" viruses, but no such requests have been made.

Recommendation (15), designed to minimize the possibility of laboratory contamination with variola virus, has been rigorously observed in both WHO collaborating centres.

DOCUMENTATION OF THE SMALLPOX ERADICATION PROGRAMME

"The eradication of smallpox is a unique event in human history and a signal achievement of WHO. It should be fully documented by the publication of a comprehensive book. Further, it is essential for future historians that all relevant documents covering matters of scientific, operational, or administrative interest should be catalogued and preserved in suitable archives. The feasibility of distributing copies of this archival material to several centres, perhaps as microfiche, should be explored.

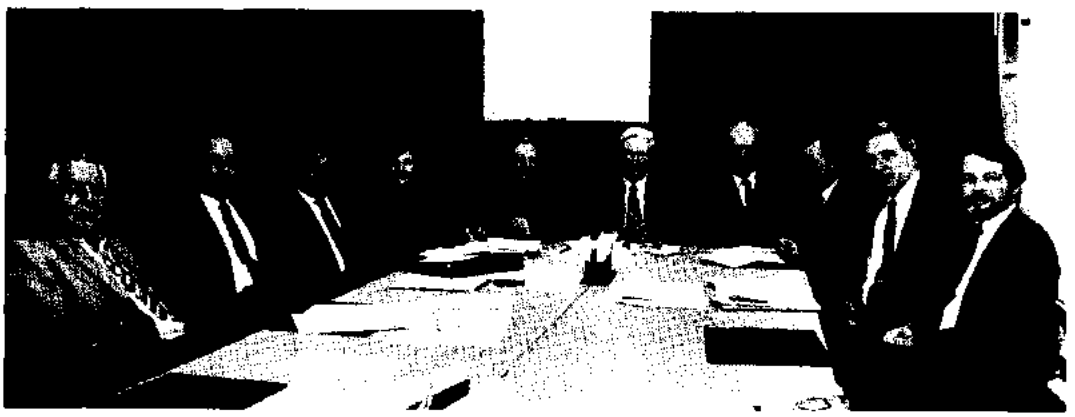
"It is important that the experiences of the smallpox eradication programme that are applicable to other health programmes should be defined and elaborated, in order to help public health officials develop strategies and tactics for the conduct of other programmes, especially those for the control of infectious diseases. However, the problem is complex since the lessons learnt from the smallpox eradication programme need to be evaluated in each instance by the health programme to which they may be applied.

"*Recommendation (16)*. WHO should ensure that appropriate publications are produced describing smallpox and its eradication and the principles and methods that are applicable to other programmes.

"*Recommendation (17)*. All relevant scientific, operational and administrative data should be catalogued and retained for archival purposes in WHO headquarters and perhaps also in several centres interested in the history of medicine."

Publications

Planning for a comprehensive publication on all aspects of smallpox and recording its eradication had in fact begun in 1979 before recommendation (16) was made, and work on the present book started early in 1980. In addition, the WHO Regional Office for



WHO / T FARKAS

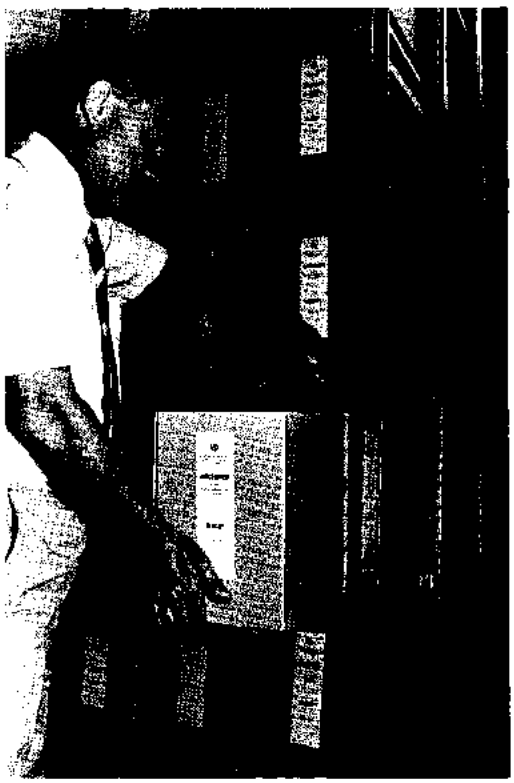
Plate 28.5. Participants in the seventh meeting of the Editorial Board for *Smallpox and its Eradication*, 26 March 1986. *Left to right:* **A.D. Loveday (WHO)**, K. Wynn (WHO), **I. Arita (Japan)**, N. Henderson (USA), S.M. Deck (WHO), **F. Fenner (Australia), I.D. Ladnyi (USSR), Z. Ježek (WHO), D.A. Henderson (USA)**, J.F. Wickett (WHO). The names of the Board members are in bold type.

South-East Asia published books dealing with the eradication programmes in India (Basu et al., 1979) and Bangladesh (Joarder et al., 1980); the government of Somalia and WHO jointly published the account of the programme in Somalia (Ježek et al., 1981); and the government of Ethiopia and the WHO Regional Office for the Eastern Mediterranean did likewise for the programme in Ethiopia (Tekeste et al., 1984). WHO also assisted in the preparation of a book dealing with the management aspects of the programme in India (Brilliant, 1985).

Recommendation (16) has also been implemented by the publication in WHO periodicals and elsewhere of numerous articles on smallpox and its eradication written by WHO staff and by other persons who were concerned with the eradication campaign. Reference to these is made throughout this book.

The Smallpox Eradication Programme Archives

The smallpox eradication programme records were put in order by a professional archivist specifically employed for the purpose in 1981–1982. All WHO records prior to 1981 are now catalogued and indexed; they occupy 400 large boxes, which are stored in the Organization's archives at WHO Headquarters. Additional material, much of it voluminous and not available elswhere, has accumulated since 1981. The Committee on Orthopoxvirus Infections suggested that it be added to the permanent archives.



WHO / M. VAN APPELGHEM

Plate 28.6. Archives of the smallpox eradication programme in WHO Headquarters, Geneva, being consulted by Ježek.

WHO HEADQUARTERS STAFF

"The foregoing recommendations cannot be carried out successfully without central coordination, which should be provided at WHO headquarters. Since it is expected that the Global Commission for the Certification of Smallpox Eradication will be dissolved after the World Health Assembly in 1980, another mechanism is needed to enable the headquarters staff to obtain advice and assistance from scientists. This could be achieved by setting up a committee on orthopoxvirus infections.

"*Recommendation (18).* An interregional team consisting of not less than two epidemiologists with past experience in the smallpox eradication campaign, plus supporting staff, should be maintained at WHO headquarters until at least the end of 1985. At least one additional field officer should be assigned to cover areas where human monkeypox is under investigation.

"*Recommendation (19).* WHO should set up a committee on orthopoxvirus infections."

Staff Arrangements at WHO Headquarters

The Smallpox Eradication unit, headed by Arita until March 1985 and then by Ježek, remained in being up to the end of 1987 with the requisite number of staff, including at various times Ježek (1980–1987), Dr A. Gromyko (1980–1983) and Dr L. Khodakevich (1983–1986) as medical officers, Mr J. Wickett (1980–1987) as consultant and Mrs S. Woolnough (1980–June 1985) as secretary. This unit, with its name unchanged, supervised the implementation of all the foregoing recommendations of the Global Commission, maintained the international rumour register, participated in the monkeypox studies in Zaire and in the preparation of publications, and organized meetings of the Committee on Orthopoxvirus Infections.

L. KHODAKEVICH, 1979

Plate 28.7. Alexander Gromyko (b. 1937), a physician from the USSR, worked for the Intensified Smallpox Eradication Programme as a WHO consultant in India in 1975 and then became a medical officer in the Smallpox Eradication unit (1977–1983). He participated in the monkeypox surveys in western Africa and in the investigation of rumours of smallpox reported to WHO.

Committee on Orthopoxvirus Infections

A group of experts, all former members of the Global Commission, met in Geneva from 3 to 5 February 1981 to discuss the implementation of the post-smallpox-eradication policy. Subsequently the Director-General of WHO appointed this group as the WHO Committee on Orthopoxvirus Infections, with Fenner as chairman. In 1984, all 6 members were appointed for a second term of 2 years.

The Committee met annually and reviewed the situation in relation to all aspects of post-eradication activities (Global Commission recommendations 1–19). In 1984 the Committee undertook a comprehensive review of the human monkeypox programme, published a report on current knowledge of the disease (*Bulletin of the World Health Organization*, 1984), and made recommendations for future activities (WHO/SE/84.162). In 1986 it reviewed the operation of the post-smallpox-eradication programme and made recommendations on all its aspects. The Committee's report was published (*Wkly epidem. rec.*, 1986b) and widely circulated; its recommendations have been discussed in the relevant sections of this chapter.

WHO / T. FARKAS

Plate 28.8. Participants in the fourth meeting of the Committee on Orthopoxvirus Infections in Geneva, 24–26 March 1986. *Left to right, front row:* **K.R. Dumbell (United Kingdom), F. Fenner (Australia), S.S. Marennikova (USSR), D.A. Henderson (USA);** *middle row:* T. Kurata (Japan), M.V. Szczeniowski (WHO), P. Brès (France), Z. Ježek (WHO), P.N. Burgasov (USSR), J. Mason (USA), Y. Ichihashi (Japan), T. Kitamura (Japan), J.H. Nakano (USA), I. Arita (Japan); *back row:* J.F. Wickett (WHO), Y.Z. Ghendon (WHO), L.N. Khodakevich (WHO), P.L. Greenaway (United Kingdom), Y.L. Reznikov (WHO). The names of the Committee members are in bold type.

USE OF VACCINIA VIRUS AS A VECTOR FOR FOREIGN GENES

The 19 recommendations made by the Global Commission in December 1979 effectively covered all aspects of orthopoxvirus infections then known to be important in the post-smallpox-eradication era. However, within 6 months, one of the members of the Global Commission, Dr K. R. Dumbell (Sam & Dumbell, 1981) discovered—and this was independently confirmed in the USA (Nakano et al., 1982)—that cells could be "transfected" with fragments of DNA from one orthopoxvirus, and that these fragments could be rescued by recombination when the cell was infected with another orthopoxvirus. It was only a short step from this to the insertion of genes coding for antigens inducing an immune response against one or more of a variety of pathogens into plasmids in such a way that they recombined with vaccinia virus. The hybrid viruses thus produced were found to express antigens whose genes had been inserted in this way, and animal experiments showed that vaccination with them conferred protection against the infections concerned. This opened up the possibility that genetically engineered vaccinia virus might be used for immunization against a wide variety of protozoal, bacterial and viral diseases (Brown et al., 1986). WHO established a Scientific Advisory Group of Experts in 1984 to guide the work of a new Programme on Vaccine Development in which developments in the use of vaccinia virus are being monitored, together with the application of genetic engineering in the production of new vaccines.

CHAPTER 29

HUMAN MONKEYPOX AND OTHER POXVIRUS INFECTIONS OF MAN

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INTRODUCTION

Human monkeypox was first recognized in 1970; it is a severe systemic disease with a generalized pustular rash, clinically indistinguishable from smallpox. In addition to variola and monkeypox viruses, 7 other species of poxvirus, of 4 genera, can cause lesions in man (Table 29.1). Although infection with each of these viruses produces at the most mild symptoms and usually only a localized skin lesion, the diseases in question presented a potential diagnostic problem during the global eradication of smallpox, since virus particles found in lesions by electron microscopic examination could be confused with those of variola virus. Because of its importance, monkeypox is the main subject of this chapter, but a brief description is given of each of the other poxvirus infections of man.

Table 29.1. Poxvirus infections of man

Genus and infection	Skin lesions in man	Severity of systemic symptoms	Host range in laboratory animals	Known reservoir hosts in nature
Orthopoxvirus				
Variola	Generalized	+++	Narrow	Man
Monkeypox	Generalized	+++	Broad	Squirrels, monkeys
Cowpox	Localized	+	Broad	Rodents
Vaccinia	Localized (very rarely, generalized)	+	Broad	Buffaloes[a]
Parapoxvirus				
Pseudocowpox	Localized	–	Narrow	Cattle
Bovine papular stomatitis	Localized	–	Narrow	Cattle
Contagious pustular dermatitis	Localized	–	Narrow	Sheep
Unclassified				
Molluscum contagiosum	Generalized	–	Narrow	Man
Tanapox	Localized	+	Narrow	Monkeys

[a] In 1984–1986, several years after the cessation of vaccination, epizootics of buffalopox were reported in several parts of India, and humans were infected. The virus involved was shown to be vaccinia virus (K. R. Dumbell, personal communication, 1986).

MONKEYPOX IN CAPTIVE PRIMATES

Monkeypox virus was discovered in 1958, when it was isolated from the lesions of a generalized vesiculo-pustular disease among captive monkeys at the State Serum Institute, Copenhagen (Magnus et al., 1959). It was apparent that if an animal reservoir of variola virus existed the eradication of smallpox would be impossible (see Chapter 10). The close resemblance between smallpox and monkeypox in captive primates focused attention on monkeypox virus as a potential threat to smallpox eradication (Arita & Henderson, 1968). WHO therefore contacted laboratories in Europe and North America which used monkeys (27 in 1968 and 51 in 1970; Arita et al., 1972), inquiring about the occurrence of monkeypox and asking specifically whether any infections had occurred among laboratory workers or animal handlers. The ensuing investigations revealed 4 other reported outbreaks and 4 hitherto unreported outbreaks in primates (Table 29.2), but there were no reports of infection in humans. Monkeypox virus was recovered in 6 of these episodes. All except episode 3 occurred in Asian monkeys, although in some outbreaks African primates (and, in episode 2, New World monkeys) were also infected.

The circumstances of these outbreaks have been summarized by Arita et al. (1972). One episode described in their paper, but omitted from Table 29.2, calls for special comment—namely, the observation made by Gispen & Kapsenberg (1966) of the National Institute of Public Health in Bilthoven, Netherlands, that monkeypox virus had been recovered from normal cynomolgus kidney cell cultures. Subsequent examination of the laboratory records led Dr J. G. Kapsenberg (personal communications, 1980, 1983) to decide that this isolation was probably due to inadvertent laboratory contamination of the culture with monkeypox virus, which had been isolated in the same laboratory at about this time from animals infected in the Blijdorp Zoo outbreak (episode 2).

Seven of the 9 outbreaks of monkeypox in captive monkey colonies between 1958 and 1968 occurred in monkeys shipped from Asia, leading to the suspicion that the reservoir of monkeypox virus was probably located in that continent. However, collaborative serological surveys organized by WHO failed to detect orthopoxvirus antibodies in over 1000 monkey sera collected in India, Indonesia, Japan and Malaysia (Arita et al., 1972). After the discovery of human monkeypox in Africa in 1970 (see later in this chapter), sera were collected from monkeys and other animals in Zaire and several countries of western Africa. Monkeypox-virus-specific antibodies were demonstrated in sera from 8 species of monkey and 2 species of squirrel, and monkeypox virus was recovered from the organs of a squirrel (see below).

Although primates from Asia, Africa and South America (and an anteater from the last-mentioned area) experienced infections with monkeypox virus in captivity, there is no evidence that the virus occurs naturally anywhere except in Africa. During the period 1958–1968 large numbers of primates were being imported into Europe and North

Table 29.2. Outbreaks of monkeypox in captive primates[a]

Country	Episode and reference	Virus isolation[b]	Date	Species affected	Origin	Interval after arrival
Denmark	1(a). Magnus et al. (1959)	+	30 June 1958	Cynomolgus	From Singapore by air	62 days
	1(b). K.L. Fennestad (personal communication, 1980)	+	7 November 1958	Cynomolgus		51 days
Netherlands	2. Peters (1966)	+	21 December 1964	Index case: giant anteater; later orang-utan, gorilla, chimpanzee, gibbon, squirrel monkey, cercopithecus, marmoset	To zoo from dealer; later animals infected by contact in Blijdorp Zoo, Rotterdam	12 days
France	3. Milhaud et al. (1969)	+	29 November 1968	Chimpanzee	Sierra Leone	11 days
USA	4. Prier et al. (1960) J.E. Prier (personal communication, 1970)	+	February 1959	Cynomolgus; later rhesus	Malaysia	"Newly arrived"
	5. McConnell et al. (1962)	+	1962	Cynomolgus; serological positives in rhesus and African green monkeys	?	9 months
	6. C. España (personal communication, 1967)	+	December 1966–March 1967	Indian and Malaysian langurs, rhesus, cynomolgus and pigtailed macaques	India, Malaysia	2 years
	7. A.H. Bruschner (personal communication, 1967)	..	November 1965	Cynomolgus	Malaysia and Philippines	?
	8. M.Z. Brierly (personal communication, 1967)	.	1966	Rhesus	India	"Recently arrived"
	9. J.H. Vickers (personal communication, 1967)	..	Before 1966	Rhesus	India	?

[a] Based on Arita et al. (1972).
[b] .. = data not recorded.

America from Asia, and smaller numbers from western Africa, mainly for the manufacture and safety testing of poliomyelitis vaccines. At that time the conditions under which monkeys were moved from their place of capture in Asia or Africa to the recipient laboratory in Europe or North America presented many opportunities for them to be infected with agents carried by other wild animals or by man while in transit (Kalter & Heberling, 1971). The cessation of outbreaks after 1968 can be ascribed to improved conditions in the shipment of primates at about that time and the much more extensive use by laboratories of monkeys bred in captivity in Europe and North America.

The clinical features of naturally occurring cases in cynomolgus monkeys have been described by Magnus et al. (1959) and Sauer et al. (1960). No signs are detected until the rash appears, usually as a single crop of discrete papules over the trunk and tail and on the face and limbs, being particularly abundant on the palms of the hands and the soles of the feet (Plate 29.1). The papules become vesicular and then pustular and are often umbilicated. Scabs develop and fall off 7–10 days after the onset of rash, leaving small scars. Circular discrete ulcers about 2 mm in diameter often occur in the oropharynx.

The severity of symptoms varied among the several different primate species infected in the outbreak of the Blijdorp Zoo in Rotterdam (episode 2, Table 29.2). All the species suffered from a generalized disease characterized by pocks on the skin, lips and mucous membranes. Orang-utans were particularly susceptible, several dying in the acute viraemic stage, before the skin lesions were fully developed.

Plate 29.1. Generalized lesions of monkeypox in a cynomolgus monkey. **A:** Acute stage; pustules on the leg and sole of the foot. **B:** Convalescent stage; healing pustules and scars. (From Magnus et al., 1959.)

THE PROPERTIES OF MONKEYPOX VIRUS

In Chapter 2 the biological characteristics of monkeypox virus have been enumerated together with those of other orthopoxviruses (Table 2.3), and the restriction endonuclease map of monkeypox virus DNA has been compared with the corresponding maps of DNAs of other species of *Orthopoxvirus* (Fig. 2.6, 2.7 and 2.9).

Pathogenicity for Laboratory Animals

Monkeypox virus has a broad host range and infects most of the common laboratory animals, producing moderate-sized haemorrhagic pocks on the chorioallantoic membrane and a large indurated swelling with a haemorrhagic centre after intradermal inoculation into rabbits (see Chapter 2, Plates 2.5 and 2.6). It produces lytic plaques in most kinds of cultured cells, but unlike variola virus, it does not grow in pig embryo kidney cells when first cultured in them, although adaptation occurs quickly.

Comparison of DNA Maps of Strains of Monkeypox Virus

Esposito & Knight (1985) analysed the DNA of 12 strains of monkeypox virus, 4 recovered from outbreaks in laboratory primates in Europe and North America and 8 from human cases in 4 countries in central and western Africa. The physical map locations of the sites of cleavage by the restriction endonuclease *Hin*dIII for the DNA of these strains of monkeypox virus, and the DNA of 2 strains each of variola and vaccinia viruses, are compared in Fig. 29.1.

As has been shown in the other comparisons described in Chapter 2, the DNAs of all strains of monkeypox virus are clearly different from those of both variola and vaccinia viruses. However, the monkeypox virus

The Nomenclature of Poxvirus Diseases

For centuries it has been traditional to name poxvirus diseases after the animals in which they were first observed—for example, cowpox, horsepox, sheep-pox and fowlpox. The practice has continued in more recent times with the use of the terms monkeypox, rabbitpox, buffalopox, elephantpox virus to designate the viral agents recovered from infections of the animals concerned. Some of these designations are misleading. Thus it now appears that "cowpox" virus is primarily a disease of rodents, which has a wide host range and occasionally infects cows, cats, zoo animals and man. Rabbitpox and buffalopox are caused by strains of vaccinia virus, propagated in series in rabbits and buffaloes respectively. And although African monkeys are infected in nature with monkeypox virus, and may indeed be an important source of infection of humans, they are probably sentinel animals, only occasionally infected with this virus, rather than its principal reservoir host.

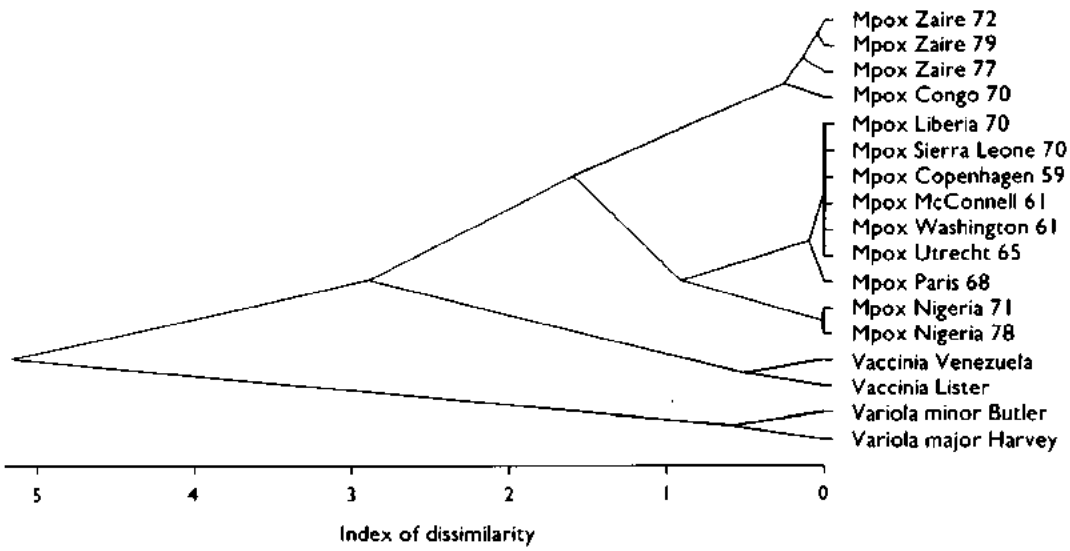


Fig. 29.1. Dendrogram illustrating the similarities and differences between the *Hin*dIII cleavage sites of the DNAs of 12 strains of monkeypox (Mpox) virus (McConnell and Washington are different passages of the same strain), 2 strains of vaccinia virus and 2 strains of variola virus. Presence, absence or impossibility of cleavage sites were analysed as described by Gibbs & Fenner (1984) using the squared Euclidean metric (number of attributes = 36). (Data from Esposito & Knight, 1985.)

DNAs cluster into 2 groups, according to the geographical origins of the specimens, rather than the animal of origin (man or monkey) or the year of isolation. The upper group of 4 in Fig. 29.1 are strains from human cases occurring in Zaire. The lower group consist of human isolates from 3 countries in western Africa—Nigeria, Liberia and Sierra Leone—and isolates from outbreaks in captive monkeys between 1959 and 1969. It is probable that all the outbreaks in captive monkeys (see Table 29.2) originated from western Africa rather than Zaire, since exports of monkeys from Africa in the late 1950s and during the 1960s were from western African countries.

Genetic Studies

Like other orthopoxviruses that produce haemorrhagic pocks on the chorioallantoic membrane, monkeypox virus produces white pock mutants. These were first observed by Bedson (1964) and first reported by Gispen &

Brand-Saathof (1972). They were shown closely to resemble the parental monkeypox virus in tests for species-specific antigen (Gispen et al., 1976) and intracellular polypeptide patterns (Harper et al., 1979).

Subsequently it was reported that variants called "whitepox" viruses, which resembled variola virus by all biological tests, could be recovered from certain laboratory stocks of monkeypox virus, either by passage in hamsters (Marennikova & Shelukhina, 1978) or by inoculation on the chorioallantoic membrane (Marennikova et al. 1979). This initially raised important questions about a possible animal reservoir of variola virus, but these were subsequently discounted. By about 1982 accumulating evidence had convinced most laboratory workers that the "whitepox" viruses were in fact strains of variola virus inadvertently introduced as laboratory contaminants (see Chapter 30).

Species Diagnosis

The biological characteristics used to identify monkeypox virus and, in material derived from human cases, to distinguish it from variola virus, are the haemorrhagic pock and high ceiling temperature on the chorioallantoic membrane, the production of a large haemorrhagic lesion after intradermal inoculation in rabbits, its wide host range and its failure to grow in pig embryo kidney cells when first inoculated into these cells. The DNA map is characteristic of the species, but can be used to distinguish western African from Zairian strains.

Serological Diagnosis of Past Monkeypox Infection

An understanding of the ecology of monkeypox virus depends either on the isolation of virus from animals captured in the field or on serological surveys for monkeypox-virus-specific antibodies. The isolation of virus from animals captured in the field is likely to be a rare event in orthopoxvirus infections, in which persistent infection does not occur, and in fact only one such isolation has been made (see below).

During the 1970s methods had been developed that enabled species-specific diagnoses of recent infection with monkeypox, vaccinia and variola viruses to be made with hyperimmune or other highly potent sera, by adsorption with appropriate viral suspensions and tests for residual antibody by gel precipitation (Gispen & Brand-Saathof, 1974), immunofluorescence (Gispen et al., 1976), radioimmunoassay (Hutchinson et al., 1977), and enzyme-linked immunosorbent assay (ELISA) (Marennikova et al., 1981) (see Chapter 3). For these tests, rather large quantities of high-titre serum were required, and for the radioimmunoassay adsorption test employed by the WHO collaborating centre in the Centers for Disease Control in Atlanta, GA, USA, antibodies to the gammaglobulin of the relevant species were thought to be necessary, which were available for monkeys but not for other species of wild animals.

However, as a result of experience with sera from persons known to have human monkeypox, some of whom had been vaccinated years earlier, Dr J. H. Nakano (personal communication, 1984) developed criteria that allowed a positive or presumptive diagnosis of monkeypox to be made in most suspected cases involving human sera. In mid-1985, Dr Nakano and Mrs Donna Miller (personal communication, 1986) developed a method of carrying out radioimmunoassay adsorption tests with sera from squirrels and some other species of wild animals, using staphylococcus A protein instead of a species-specific anti-gammaglobulin. This made it possible to test many animal sera from the field and has helped to elucidate the ecology of monkeypox virus.

HUMAN MONKEYPOX

Discovery of Human Infections

The first case of human monkeypox was found in the Basankusu Hospital, Equateur Province, Zaire (Ladnyj et al., 1972). The Basankusu Zone covers an area of about 20 000 square kilometres and in 1970 had an estimated population of 62 000, mostly primitive farmers and hunter-gatherers living in small villages in dense tropical rain forest. The last known outbreak of smallpox in Basankusu Zone occurred in 1968 and comprised 70 cases with 18 deaths. Several suspected cases of smallpox were treated at the hospital in 1969, but none was confirmed. Two suspected cases were reported in 1970; one of these turned out to be chickenpox, and the other was the first case of human monkeypox to be detected. The patient, a 9-month-

old boy, became ill with fever on 22 August 1970 and a rash developed 2 days later. He was admitted to hospital on 1 September, the 9th day of the rash, which had the characteristic centrifugal distribution of smallpox. Crusts were collected for laboratory examination and sent through WHO in Geneva to the WHO collaborating centre in the Moscow Research Institute for Viral Preparations, USSR. The patient recovered and was about to be discharged, but on 23 October he developed measles (acquired while in hospital) and died 6 days later.

During 1970 the WHO collaborating centre in Moscow had received a number of specimens from various provinces of Zaire (but not from Equateur Province) from which variola virus had been recovered. The virus from Basankusu Hospital produced pocks on the chorioallantoic membrane that were quite different from those of variola virus. More detailed studies of this isolate, including inoculation in rabbit skin, showed that it was monkeypox virus (Marennikova et al., 1972a). Investigations of the epidemiological circumstances of the patient by Ladnyi and Dr P. Ziegler in 1971 revealed that the child was the only unvaccinated member of his family, and that there had been no other cases of fever with rash recently in the village concerned or in neighbouring villages. Such an isolated case was most unlikely to be smallpox.

The discovery of human monkeypox in central Africa in September 1970 was followed by the demonstration that 4 cases of suspected smallpox in Liberia and 1 case in Sierra Leone in 1970, and 1 each in Nigeria and Côte d'Ivoire in 1971 (Foster et al., 1972) were cases of human monkeypox (Lourie et al., 1972). A series of coordinated laboratory and field studies was organized to determine the incidence of the disease, to study its clinical features and epidemiology and to search for the animal reservoir or reservoirs of the virus.

Organization of Laboratory Research

In order to obtain guidance on what further research might be undertaken on the

Plate 29.2. Meeting of the Informal Consultation on Monkeypox and Related Viruses, Geneva, February 1976. *Left to right, front row:* T. Kitamura (Japan) C.I. Sands (WHO), C. Algan (WHO), F. Fenner (Australia), I. Arita (WHO), J.H. Nakano (USA); *middle row:* J.G. Breman (USA), R. Netter (France), E.A. Smith (Nigeria), S.S. Kalter (USA), I.D. Ladnyi (USSR), H.S.Bedson (UK), S.S. Marennikova (USSR), A.N. Slepushkin (WHO); *back row:* M.V. Szczeniowski (WHO), E.S. Johnson (Sierra Leone), B. Guyer (USA), N. French (USA), I. Tagaya (Japan), W.K. Joklik (USA), D.A. Henderson (WHO), K.R. Dumbell (UK), V.N. Mitushin (USSR), A.C. Hekker (Netherlands).

Recognition of Human Monkeypox in Central and Western Africa

Virologists interested in the poxviruses had known since 1959 that monkeypox virus could cause a generalized disease resembling smallpox in cynomolgus monkeys, and in the 1960s similar cases were recognized among other species of monkeys and in anthropoid apes. Although animal handlers had been exposed to risk during the several outbreaks among laboratory and zoo primates during the 1960s, there was at this time no indication that monkeypox virus would infect humans.

At the first meeting of the WHO Informal Group on Monkeypox and Related Viruses, in Moscow in March 1969, the experts agreed that the first indication that virus recovered from a skin lesion might be monkeypox virus would be the haemorrhagic appearance of the pocks produced on the chorioallantoic membrane after 3 days' incubation at 35 °C.

On 23 September 1970 Dr S. S. Marennikova, Dr E. M. Shelukhina and Dr N. N. Maltseva, of the WHO collaborating centre in Moscow, recovered a virus on the chorioallantoic membrane from material sent from a patient in Zaire. When examined after incubation for 2 days, the pocks were "perfectly typical" of variola virus. However, after another day's incubation at 35 °C, there was some haemorrhage around the pocks, a feature never seen with variola virus and characteristic of monkeypox virus. Further tests showed that, like monkeypox virus and unlike variola virus, the Zaire isolate produced large lesions in the rabbit skin.

Meanwhile, a diagnosis of variola virus had been made in the WHO collaborating centre in Atlanta with material obtained from 2 cases of smallpox-like disease discovered in different parts of Liberia in mid-September. This diagnosis caused great concern, since Liberia was thought to have been free of smallpox since 1969. Having learned of the occurrence of human monkeypox in Zaire, Henderson suggested to the WHO collaborating centre in Atlanta that the Liberian isolates should be carefully examined by appropriate tests to see whether they might be monkeypox virus. The Liberian isolates, and subsequent isolates from Sierra Leone and Nigeria, were then found to have the characteristics of monkeypox virus (Lourie et al., 1972).

Arrangements were made for further examination of both the Zaire and the Liberian isolates by Dr Keith Dumbell in London and Dr Rijk Gispen in Bilthoven, as well as in the WHO collaborating centres in Atlanta and Moscow. Work on these isolates formed the main topic of discussion at the second meeting of the Informal Group on Monkeypox and Related Viruses in February 1971. The experts attending that meeting agreed that these isolates were indeed monkeypox virus. This conclusion was a source of considerable relief, since it excluded the possibility that smallpox had been recurring in the most unlikely epidemiological situations; yet it also caused some concern, in that a new generalized orthopoxvirus disease of man had been discovered, the public health importance of which was unknown.

problem of monkeypox and to find out whether there was any evidence of an animal reservoir of variola virus, the WHO Smallpox Eradication unit organized informal discussions on monkeypox virus studies among a group of virologists, which met first in Moscow from 26 to 31 March 1969. These experts agreed that monkeypox virus could be readily distinguished from variola and vaccinia viruses by its biological characteristics, and further studies were planned on its morphology and behaviour in experimentally infected primates, and on the use of serological tests to determine its geographical distribution.

The discovery of human monkeypox, and the subsequent reports that a variola-like virus ("whitepox" virus) had been recovered from the organs of animals captured in areas of Africa in which human monkeypox cases had occurred (see Chapter 30), clearly called for expert advice from virologists. Further meetings of the Informal Group on Monkeypox and Related Viruses were therefore arranged. In all, 5 more meetings were held, in 1971, 1973, 1976, 1978 and 1979, and were

attended by a total of 32 scientists from laboratories in 10 countries, including the WHO collaborating centres in Atlanta and Moscow as well as other collaborating centres conducting poxvirus research, in Bilthoven, Birmingham, London, Paris and Tokyo. In addition, field workers from 5 countries in central and western Africa and representatives from the WHO Regional Office for Africa, in Brazzaville, Congo, attended some of the meetings. Laboratory research on monkeypox, variola and "whitepox" viruses was carried out in the laboratories of the scientists who attended the meetings, sometimes with financial assistance from WHO.

Organization of Field Research

To determine the most effective way of conducting the field research, the Smallpox Eradication unit organized a coordination meeting of representatives from central and western African countries in the WHO Regional Office for Africa, in October 1976, to assess the epidemiological situation in relation to human monkeypox, to draw up procedures for field surveys and to assess the sensitivity of epidemiological surveillance. It was clear from the data presented at this meeting that the best surveillance programme was that conducted in Zaire, the only country in the region in which smallpox surveillance had been maintained until eradication was certified in 1977 (see Chapter 25). Following a recommendation of the coordination meeting, an intensive surveillance programme was set up under the leadership of Dr Kalisa Ruti of the Ministry of Health of Zaire and Mr M. Szczeniowski, a WHO technical officer, in a geographically limited area in the northern part of Zaire (Equateur Region, Mongala Subregion), in which a high concentration of human monkeypox cases had been observed.

This activity was extended in 1979–1980; and in May 1980 the Thirty-third World Health Assembly accepted the recommendation of the Global Commission for the Certification of Smallpox Eradication that further research was needed to determine the public health importance of human monkeypox. Field activities in Zaire were strengthened (see Chapter 28), and laboratory support was provided by the WHO collaborating centres in Atlanta and Moscow. The description in the following pages of the clinical features and epidemiology of human monkeypox and the ecology of monkeypox virus is based on these studies, carried out over approximately a decade but most intensively in the years 1982–1986.

Incidence and Distribution

Just over 400 cases of human monkeypox were reported between 1980 and 1986, all of which occurred in tropical rain forest areas of central and western Africa. At the time of writing, detailed analyses were available of the 283 cases reported between 1970 and 1984 (Fig. 29.2; Table 29.3). Of these, 89% were in small villages (under 1000 inhabitants) and 10% in larger villages (1000–5000 inhabitants); only 3 cases were reported in towns of over 5000 inhabitants. Even the last-named population groups had ample opportunities for direct contact with animals killed in the rain forests.

Between 1972 and 1981, the cases reported from Zaire greatly outnumbered those reported from any other country (Table 29.3), probably because the number of people living in villages in tropical rain forests is much larger there. From 1982 onwards many more cases were reported from Zaire than in previous years. This was partly due to the intensive surveillance system that had been developed in enzootic foci in that country,

Z. JEŽEK, 1981

Plate 29.3. Mark V. Szczeniowski (b. 1944), a former United States Peace Corps volunteer, joined WHO in 1971 and worked as a leader of one of the mobile smallpox surveillance teams in Zaire. From 1980 he participated in the epidemiological surveillance of human monkeypox and viral haemorrhagic fevers in that country.

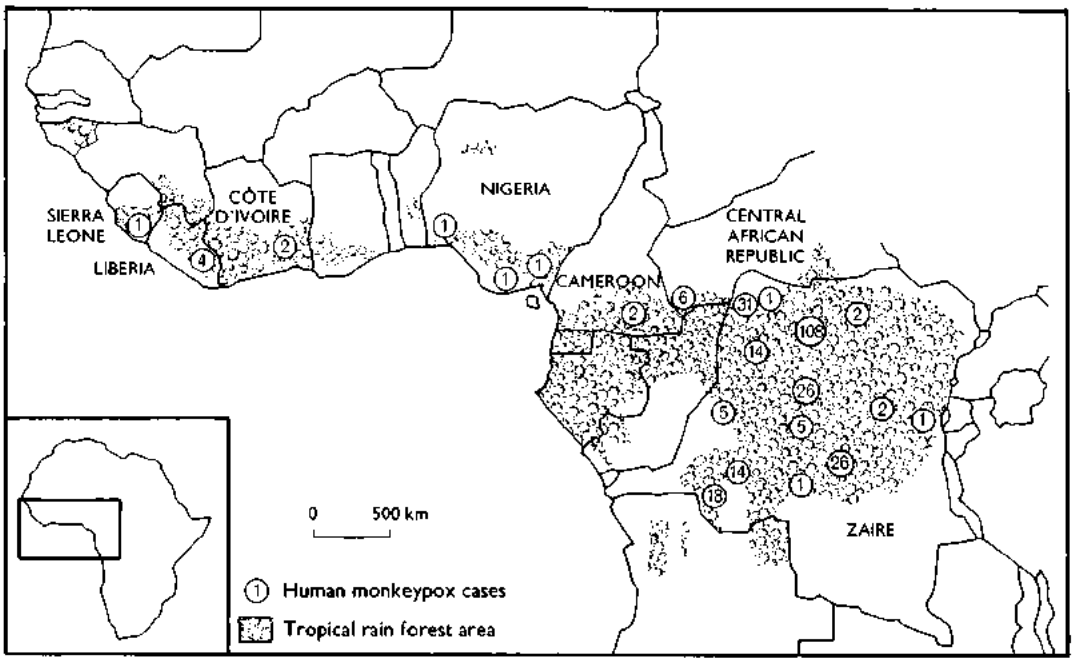


Fig. 29.2. Western and central Africa, showing the extent of tropical rain forest and the locations where cases of human monkeypox have occurred, 1970–1984.

Table 29.3. Human monkeypox: areas of tropical rain forest and annual numbers of cases reported in countries in western and central Africa, 1970–1984

	Cameroon	Central African Republic	Côte d'Ivoire	Liberia	Nigeria	Sierra Leone	Zaire	Total
Area of rain forest: 1980 (thousands of hectares)[a]	17 920	3 590	4 458	2 000	5 950	740	105 650	140 308
Percentage of all rain forests in western and central Africa[b]	9.5	1.9	2.4	1.1	3.2	0.4	56.2	74.7
Number of cases of monkeypox in:								
1970	0	0	0	4	0	1	1	6
1971	0	0	1	0	2	0	0	3
1972	0	0	0	0	0	0	5	5
1973	0	0	0	0	0	0	3	3
1974	0	0	0	0	0	0	1	1
1975	0	0	0	0	0	0	3	3
1976	0	0	0	0	0	0	5	5
1977	0	0	0	0	0	0	6	6
1978	0	0	0	0	1	0	12	13
1979	2	0	0	0	0	0	8	10
1980	0	0	0	0	0	0	4	4
1981	0	0	1	0	0	0	7	8
1982	0	0	0	0	0	0	40	40
1983	0	0	0	0	0	0	84	84
1984	0	6	0	0	0	0	86	92
Total number of cases	2	6	2	4	3	1	265	283

[a] Source: Food and Agriculture Organization of the United Nations (1981).
[b] Areas of rain forest (25.3% of total) occur in 6 countries of western and central Africa in which human monkeypox has not been reported.

but there appears to have been a real increase in the incidence in 1983 and 1984. The reason for this increase is still uncertain. It may have been attributable in part to the fact that there were many more unvaccinated children than in earlier years, and in part, perhaps, to fluctuations in the extent of infection in the animals from which human infections were acquired.

Clinical Features

A description of the clinical features of human monkeypox based on 47 cases diagnosed up to the end of 1979 (Breman et al., 1980) needs little revision in the light of experience since then (Arita et al. 1985). Clinically, human monkeypox closely resembles discrete ordinary-type or, occasionally, modified-type smallpox, as described in Chapter 1. No case has yet been seen, among the cases diagnosed in the years 1970–1984, with confluent lesions on the face, nor has any case comparable to flat-type or haemorrhagic-type smallpox been diagnosed. The obvious clinical feature that differentiates human monkeypox from smallpox is the pronounced lymph-node enlargement seen in most cases of monkeypox (Plates 29.4 and 29.5), sometimes only in the neck or inguinal region, but more often generalized. Lymph-node enlargement occurs early, and has often been observed at the time of onset of fever, usually 1–3 days before the rash appears. Lymph-node enlargement was observed in 90% of 98 cases in which its presence or absence was recorded and was a presenting sign, preceding the rash, in 65% of these cases.

The eruption begins after a prodromal illness lasting 1–3 days, with fever, prostration and usually lymph-node enlargement. As with smallpox, the lesions develop more or less simultaneously and evolve together at the same rate, through papules, vesicles and pustules, before umbilicating, drying and desquamating. This process usually takes about 2–3 weeks, depending on the severity of the disease. The distribution of the rash is mainly peripheral. Severe eruptions can cover the entire body (Plate 29.4), including the palms and soles. Most pustules are about 0.5 cm in diameter but some have been seen up to 1 cm in diameter. Lesions have been noted on the mucous membranes, the tongue and genitalia. One patient, who had been vaccinated several years previously, developed only 1 lesion, further emphasizing the fact that some cases can be exceedingly mild and would go unreported in the absence of active surveillance. As is described below, subclinical cases also occur, in unvaccinated as well as vaccinated subjects.

Sequelae

As in smallpox, pitting scars may develop, most frequently on the face, but they tend to diminish in prominence with time. Secondary infection of the lesions is common and this may play a role in scarring. About half of the scars from lesions seen initially on the face and body were detectable 1–4 years after the acute illness. Desquamation of crusts leaves areas of hypopigmentation (Plate 29.5 B). Hyperpigmentation follows after a few months (Plate 29.4 D) and usually diminishes with time. In some cases large shallow residual scars are seen, and in a few cases corneal lesions have caused unilateral blindness.

Laboratory confirmation

Throughout the investigations, great importance was attached to obtaining laboratory confirmation of the clinico-epidemiological diagnoses, initially because of the possible occurrence of smallpox and later because of the suspicion that "whitepox" virus (see Chapter 30) might infect humans. All laboratory diagnoses were made in the WHO collaborating centres, with the results shown in Table 29.4. The methods of laboratory diagnosis were those used for smallpox, supplemented by serology in cases in which viral isolation was not possible. This combination allowed positive diagnoses to be made in the great majority of cases. In spite of unavoidable delays in the collection and transmission of specimens, the percentage of recoveries of virus from samples taken from cases eventually diagnosed as human monkeypox was high. Virtually all the cases found positive by electron microscopy were also found positive by culture, and vice versa, but 60 (22%) of the cases were seen too late to obtain lesion material and could only be confirmed serologically. Retrospective diagnosis by serology was unequivocal in unvaccinated subjects but sometimes less clear in vaccinated persons, although with the experience gained over the past few years diagnoses are now possible in these cases also.

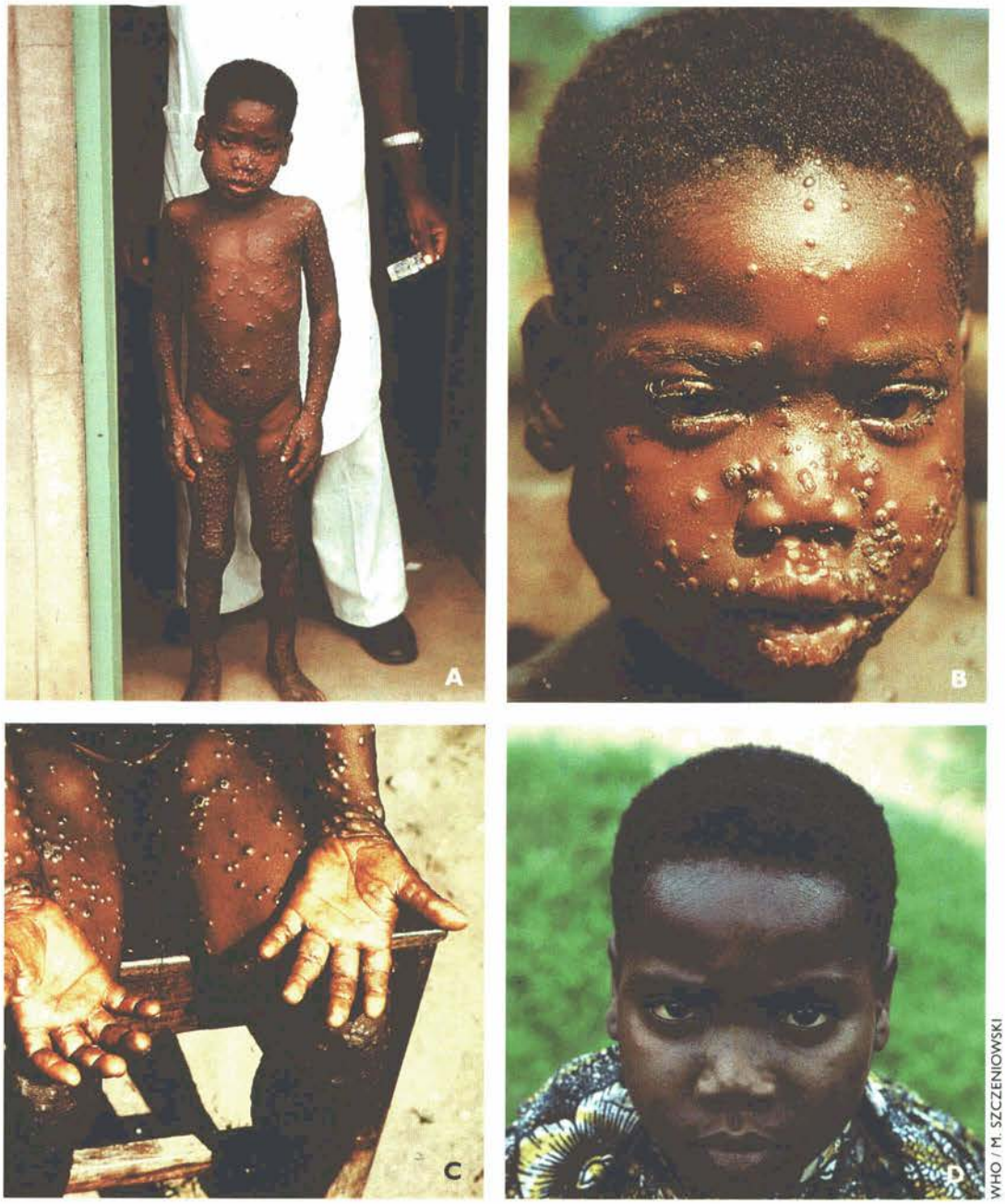
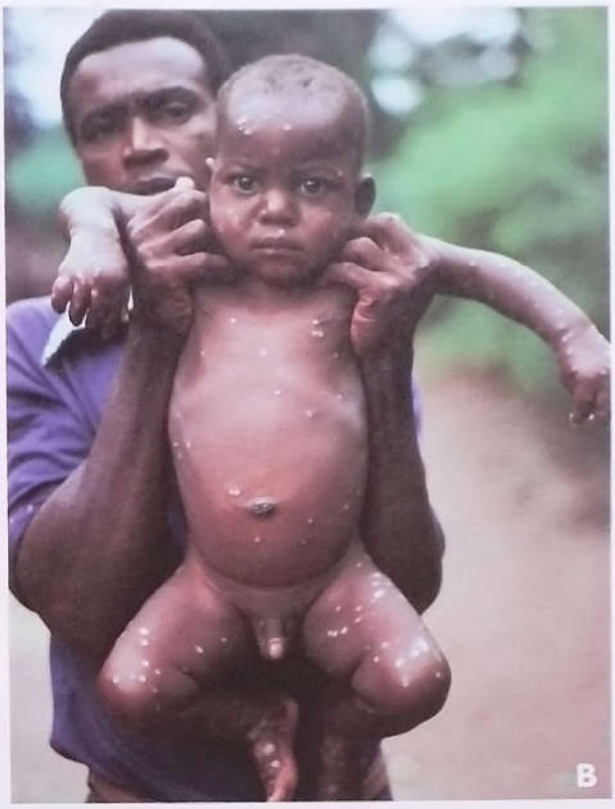


Plate 29.4. Human monkeypox in a 7-year-old Zairian girl. **A, B, C:** Acute stage, day 7 of rash. Note bilateral inguinal lymphadenopathy and enlarged submaxillary lymph nodes on right side. Pustular lesions on lips (**B**) also occur inside the mouth as ulcerated lesions: the enanthem. **D:** Same subject, 4½ years later. There are several hyperpigmented spots and facial pockmarks; in about half the cases of monkeypox these disappear within 5 years of the attack.



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F. MEIER

Plate 29.5. **A:** Human monkeypox: 3-year-old Zairian boy with rash in the scabbing stage. Axillary lymph nodes are still enlarged. **B:** Human monkeypox: 1-year-old Zairian boy, day 24 of rash. There are depigmented spots where the scabs have come off. Inguinal lymphadenopathy is still present. **C:** Typical tropical rain forest in a region in Zaire where cases of human monkeypox have occurred.

Plate 29.6. Cowpox, pseudocowpox and orf in animals and in humans. **A:** Cowpox ulcer on teat of a cow, 7 days after onset of symptoms. **B:** Pseudocowpox (milker's nodule virus) on teat of a cow. **C:** Scabby mouth caused by orf virus, in a lamb. Photographs on the right show lesions caused by these viruses on the hands. **D:** Cowpox. **E:** Pseudocowpox (milker's nodule). **F:** Orf.

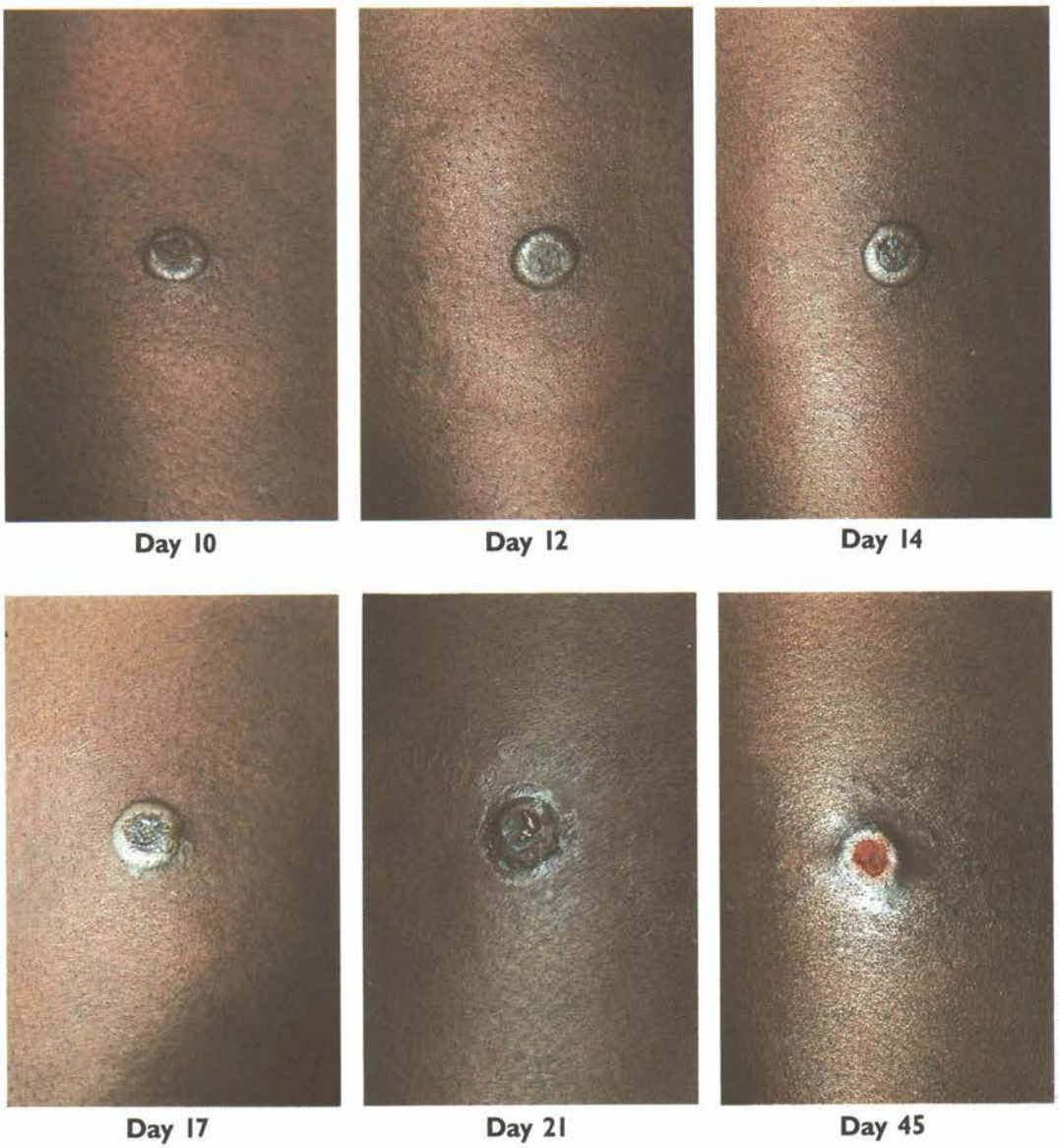

Plate 29.7. Tanapox. Lesion on the thigh of a Zairian woman aged 27 years, 10, 12, 14, 17, 21, and 45 days after its appearance. Note slow progression, pronounced surrounding oedema and erythema during the first 2 weeks, and eventual ulceration and healing.

Table 29.4. Number of positive results of laboratory tests in cases clinically diagnosed as human monkeypox, 1970–1984

Period	Electron microscopy	Chorioallantoic membrane inoculation	Serology
1970–1977	22	21	25
1978–1981	23	20	25
1982–1983	70	71	73
1984	57	67	53
Total	172	179	176

Severity and case-fatality rates

On the basis of the number of skin lesions and the severity of systemic symptoms, cases in Zaire were classified as mild, moderate or severe (Table 29.5). The majority of cases (53.1%), and the majority of severe cases among the unvaccinated (58.3%), occurred among unvaccinated children in the age group 0–4 years. The 28 deaths all occurred in children between 7 months and 7 years of age (overall case-fatality rate among unvaccinated subjects, 11.3%), the case-fatality rate for the age group 0–4 years (14.3%) being almost twice that in unvaccinated children aged 5–14 years (7.7%).

Few cases were diagnosed in vaccinated subjects, only 30 of the 277 patients (10.8%) having a visible vaccination scar. The youngest of these was a 5-year-old boy who had been vaccinated shortly after birth and developed monkeypox late in 1983—i.e., about 5 years after vaccination.

Subclinical infections

Some cases of monkeypox in vaccinated subjects were extremely mild, with very few skin lesions. By analogy with smallpox (Heiner et al., 1971a; see Chapter 1), it was to be expected that many infections in vaccinated subjects would be subclinical. A more important question was whether inapparent infections occurred in unvaccinated human subjects. Data pertaining to this problem emerged from the intensive surveillance activities in Zaire in 1982–1984 (Ježek et al., 1986b). During that period 2510 contacts of 131 confirmed cases of human monkeypox were examined and questioned, often on several occasions. Sera were taken from 70% of the unvaccinated contacts and 6% of the vaccinated contacts and tested at the WHO collaborating centres in Atlanta and Moscow (Table 29.6). The laboratory tests showed that 91 (16%) of the contacts examined had been infected with monkeypox virus. Sixty of the 73 cases in unvaccinated contacts had a history or lesions compatible with human monkeypox, and 40 of them appeared to be secondary cases resulting from transmission of infection from another human case. The other 13 unvaccinated subjects (18%) gave no history and had no lesions suggestive of human monkeypox and must therefore be classed as cases of subclinical infection. The majority of such cases occurred in children aged between 2 and 10 years who had been household contacts of a severe case of human monkeypox. Only 1 subclinical case was recognized in a vaccinated subject, a 20-year-

Table 29.5. Human monkeypox in Zaire, 1970–1984: vaccination status, age distribution of unvaccinated patients and severity of illness (including deaths)[a,b]

Vaccination scar	Age group (years)	Clinical severity									
		Mild		Moderate		Severe				Total	
						Recovered		Fatal			
		Number	%	Number	%	Number	%	Number	%	Number	%
Absent	⩽4	11	7.5	38	25.8	77	52.4	21	14.3	147	59.5
	5–14	8	8.8	16	17.6	60	65.9	7	7.7	91	36.8
	⩾15	3	33.3	3	33.3	3	33.3	0	–	9	3.7
	Total	22	8.9	57	23.1	140	56.7	28	11.3	247	100
Present or doubtful	All ages	16	53.3	5	16.7	9	30.0	0	–	30	100

[a] Number of cases and deaths by percentages of all cases in unvaccinated and vaccinated groups respectively.

[b] Mild: less than 25 skin lesions; no incapacity and no need for special care. Moderate: 25–99 skin lesions; incapable of most physical activity but not requiring nursing care. Severe, non-fatal: 100 or more skin lesions; fully incapacitated and requiring medical care. Fatal: deaths due to monkeypox, usually occurring in "severe" cases.

Table 29.6. Evidence of infection with monkeypox virus among close contacts of cases of human monkeypox in Zaire, 1982–1984[a]

Vaccination scar	Contacts			Laboratory evidence of monkeypox			
	Type	Number examined	Laboratory tests	Total number	Clinical disease		Subclinical infection
					Co-primary case	Secondary case	
Absent	Household	277	198	49	13	29	7
	Other	364	251	24	7	11	6
	Total	641	449	73	20	40	13
Present	Household	910	71	15	1	14	0
	Other	959	39	3	0	2	1
	Total	1 869	110	18	1	16	1

[a] Based on Ježek et al. (1986b).

old man, but no special effort was made to detect subclinical infections among vaccinated subjects in a way comparable to the studies of Heiner et al. (1971a) with variola major in Pakistan.

Large-scale serological surveys of unvaccinated persons in Zaire (Ježek et al., 1987a; see later in this chapter) also revealed a few cases of subclinical infection.

Epidemiology

Although the clinical features of human monkeypox are very similar to those of discrete ordinary-type smallpox, the epidemiology is quite different. Human monkeypox occurs mainly as single or occasionally multiple sporadic cases, in small villages in dense tropical rain forest in a limited part of Africa, among villagers who are engaged for at least part of their time as hunters and gatherers. Human monkeypox is a zoonosis which is usually contracted from a wild animal. However, human-to-human infection does occur in a minority of cases.

Two observations in the early 1980s deserve comment. Mutombo et al. (1983) reported a bizarre case in which a 6-month-old infant in a small village in the tropical rain forest in Zaire was abducted by a chimpanzee but rescued after sustaining a superficial wound on the lower leg and a fractured femur. The infant developed typical monkeypox, fever beginning 6 days after the incident and a rash 7 days later. Monkeypox virus was isolated from crust material. Lymphadenopathy began in the left inguinal region and eventually became generalized, but the time of its appearance in relation to other symptoms could not be determined. Although not proved, it is a reasonable hypothesis that the infant acquired monkeypox from the chimpanzee.

The other observation concerns monkeypox among Pygmies who live in the tropical rain forests in the southern part of the Central African Republic, adjoining Zaire, in which Khodakevich et al. (1985) discovered a cluster of 5 cases of monkeypox, confirmed by virus isolation. The Pygmies who lived in the rain forests readily recognized the disease when shown a monkeypox recognition card, whereas the Bantus and Pygmies who lived in agricultural settlements had never seen a disease like it. Interrogation through interpreters revealed that the forest Pygmies had a special name for the disease and believed that it was acquired from animals and not from humans.

Age and sex distribution

The ages of patients in Zaire varied between 6 months and 53 years, but the majority were children. The two sexes were equally affected; of 283 cases reported by the end of 1984, 51.3% were in males and 49.7% in females. When analysing the epidemiology of human monkeypox it is useful to distinguish between infections acquired from an animal source (primary cases) and those due to person-to-person infection (secondary cases) (Table 29.7). The vast majority of cases in both groups occurred in children, but cases in adults tended to be more

Table 29.7. Human monkeypox: the age incidence of primary and secondary cases in Zaire, 1982–1984

Age group (years)	Primary cases[a]		Secondary cases[b]	
	Number	%	Number	%
0–2	41	28.3	21	31.8
3–4	36	24.8	11	16.7
5–9	55	38.3	17	25.7
10–14	7	5.0	6	9.1
⩾15	5	3.6	11	16.7
Total	144	100.0	66	100.0

[a] Presumed to have been infected from an animal source.
[b] Presumed person-to-person infection.

common among persons infected by contact with other human cases, usually mothers infected by sick children.

Seasonal distribution

Breman et al. (1980) reported a preponderance of cases in Zaire in the dry season, but with the institution of more intensive surveillance since 1982 the incidence of cases has been found to be much the same throughout the year. During the period 1982–1984 the monthly incidence of primary cases varied a good deal from year to year (Table 29.8); there was no clearly evident seasonal pattern. Secondary cases showed the same absence of a seasonal effect, although, as with primary cases, the incidence was low in October.

Sources of infection of sporadic cases

Epidemiological investigations in Zaire indicated that wild animals were the probable source of infection for some 70% of patients, and person-to-person infection was suspected in the remaining 30% (see Table 29.8). Since monkeypox virus has a wide host range and evidence of infection in African wild animals has been obtained from chimpanzees, several species of monkey and 2 species of squirrel, the disease is probably transmitted to humans by more than one species of wild animal. It was virtually impossible to determine by case-control studies which animals might have been involved because the whole population in affected localities had multiple daily contacts with the same varieties of wild animals, in the settlements, agricultural areas or nearby forests. Species with which patients had multiple close contacts (within 3 weeks before the onset of rash), through hunting, skinning, playing with the animals or eating the carcasses, included various types of monkeys (65%), squirrels (12%), antelopes and gazelles (12%), terrestrial rodents (9%) and other animals (3%). Seventy-one per cent of suspected monkeys associated with patients belonged to the genus *Cercopithecus*, 12% to *Colobus* and 8% to *Cercocebus*. Two-thirds of suspected rodents were squirrels and the rest were Cricetidae. The majority of animals suspected of being the source of infection were apparently healthy.

The small villages in tropical rain forests, in which cases of human monkeypox occur, are usually not closely surrounded by high forest on all sides. A common situation is that they consist of groups of houses along roads through the forests, with extensive agricultural areas around the settlement itself, consisting of gardens and secondary forest, often with many oil palms, which provide food much favoured by certain squirrels. Beyond this, perhaps 3–5 kilometres away, is the primary rain forest. Each of the 3 zones—settlement, agricultural area, and forest—has a characteristic fauna. Domestic animals and commensal rodents frequent the immediate

Table 29.8. Human monkeypox: monthly incidence of primary and secondary cases in Zaire, 1982–1984, calculated from date of onset

Year	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
Primary cases													
1982	5	0	0	0	1	2	4	1	3	2	2	4	24
1983	0	1	3	2	7	5	8	6	9	2	6	9	58
1984	6	8	11	4	9	9	3	4	5	2	1	0	62
Total	11	9	14	6	17	16	15	11	17	6	9	13	144
Secondary cases													
1982–1984[a]	3	7	5	4	4	3	6	10	7	2	5	10	66

[a] Numbers of cases too small to justify providing annual data.

Table 29.9. Human monkeypox: occurrence of primary and secondary cases in Zaire, 1982–1984

Year	Primary cases[a]		Person-to-person infection		Total
	Isolated primary case	Presumed co-primary case	Presumed secondary case	Presumed tertiary or later case	
1982	20	4	13	3	40
1983	37	21	19	7	84
1984	43	19	17	7	86
Total	100 (47.6%)	44 (21.0%)	49 (23.3%)	17 (8.1%)	210

[a] Presumably infected from an animal source.

environs of the houses, terrestrial and arboreal rodents and bats are found in the agricultural areas, and larger animals, including monkeys, inhabit the rain forest itself (Khodakevich et al., 1987a).

The various age groups of the population differ in the degree to which they move in and out of these areas. Children below the age of 2 years are rarely let out of their mother's sight; between the ages of 3 and 5 years they accompany their mothers to the agricultural area, and after the age of 5 years they go on their own to this area and hunt for small animals. Only the men and boys over 15 years of age hunt in the forest for large animals, including monkeys, antelopes and porcupines. Persons of all age groups would be exposed to infection from wild animals brought to the household for food. Those who might conceivably be exposed to an additional risk are the hunters and children old enough to capture small animals such as squirrels and rats in the agricultural areas. Very few primary cases have occurred in hunters, whereas children aged between 5 and 9 years have contracted many primary infections but a somewhat lower proportion of secondary infections (see Table 29.7). This may be related to the relatively high incidence of infection among squirrels captured in the agricultural areas (see below).

Person-to-person spread

The largest proportion of cases of monkeypox (48%) have occurred as single sporadic infections. However, sometimes cases have occurred in clusters, suggesting either multiple infections from a common source—co-primary cases—(if the dates of onset lay within the presumed minimum incubation period of 7 days) or person-to-person transmission. The distribution of single sporadic cases, presumed co-primary cases and presumed secondary or subsequent person-to-person infections in Zaire in 1982–1984 is shown in Table 29.9. Intervals of 7 and 23 days between the dates of appearance of the rashes in persons in close family contact have been taken as the limits for presumed person-to-person spread. In the 3 years during which intensive surveillance was operating in Zaire, 66 out of 210 cases (31.4%) appeared to have been due to transmission from person to person. Examples of the type of pattern observed are shown in Fig. 29.3. An extreme example involving 4 probable successive person-to-person infections has been described by Ježek et al. (1986a).

If all these presumed cases of person-to-person infection are accepted as such, the secondary and later generation attack rate was 15.7% among unvaccinated household contacts and 0.6% among vaccinated household contacts. The secondary and later generation attack rate among those having casual face-to-face contact with patients was 3%. These figures are much lower than those for smallpox, in which the overall first generation secondary attack rates in household contacts were 58.4% for unvaccinated persons and 3.8% among vaccinated contacts (see Chapter 4, Table 4.12).

Using these data, which were obtained from a population in which the vaccination rate was about 70%, Ježek et al. (1987b) developed a stochastic model for person-to-person infections with monkeypox virus assuming overall vaccination rates of 50%, 25%, and zero. Although the expected numbers of generations and of cases infected by contact increased with the falling vaccination rate, the model suggested that the person-to-person infectivity of monkeypox was such that the disease always died out, after a maximum number, in the simulation,

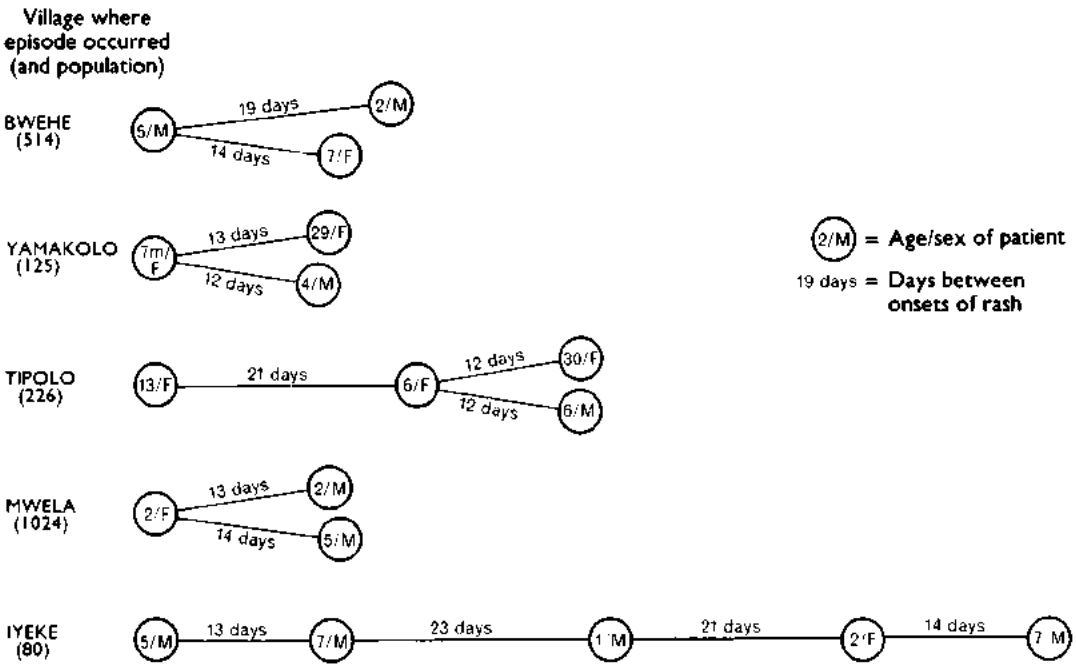

Fig. 29.3. Some examples of presumed person-to-person transmission of monkeypox. All occurred among close family contacts, who lived in small villages in the tropical rain forest. Assuming that patients could remain infectious for about a week after the onset of the rash, the intervals between cases could be longer than the usual incubation period (assumed to be about 12 days, with a range of 7–19 days).

of 11 generations. This result supports an argument based on historical data—namely, that monkeypox virus has been enzootic in animals of the tropical rain forests in Zaire for centuries without ever establishing continuous person-to-person infection in a population that had been almost completely unvaccinated until about 1967.

The prevalence of monkeypox virus infection in humans

In an attempt to discover the prevalence of monkeypox virus infection of humans in tropical rain forest areas in various parts of central and western Africa, serological surveys of persons without vaccination scars were carried out in 1981 in the Congo and Zaire (central Africa) and Côte d'Ivoire and Sierra Leone (western Africa), according to a plan designed by Arita and Dr Joseph McCormick. Cases of monkeypox had been reported from all these countries except the Congo, which borders on Zaire and has a large area (over 21 million hectares) of tropical rain forest. Specimens of serum collected from allegedly unvaccinated persons were tested in the WHO collaborating centres in Atlanta and Moscow, initially for vaccinia haemagglutination-inhibiting (HI) antibody, or by immunofluorescence at the Pasteur Institute in Abidjan, Côte d'Ivoire.

The results are shown in Table 29.10. Of 10 300 sera tested, 15.4% gave positive results by HI or immunofluorescence tests.

Supplementary examination of many of these sera by neutralization and ELISA tests showed good agreement with the results obtained with the HI or immunofluorescence test. The intention was to subject sera containing orthopoxvirus antibodies demonstrable by the screening test to further assay by either a radioimmunoassay adsorption test or an ELISA adsorption test. However, only 420 of the 1583 positive sera could be tested; of these, 73 gave results indicating that the subjects had been infected with monkeypox virus. None of the sera from the Congo gave a positive result by the ELISA adsorption test; the proportions of all sera designated as monkeypox-virus-positive varied from 0.70% for Côte d'Ivoire to 1.01% for Sierra Leone.

Table 29.10. Human monkeypox: results of serological survey among allegedly unvaccinated persons inhabiting villages in tropical rain forest areas of 4 countries of central and western Africa, 1981

Country	Number of sera tested	Positive by haemagglutination-inhibition or immunofluorescence test		Positive for monkeypox virus antibodies by radioimmunoassay adsorption		
		Number	Percentage	Number tested	Number positive	Percentage of total sera
Congo	1 433[a]	231	16.1	78[b]	0	0.0
Côte d'Ivoire	2 840	369	13.0	93	20	0.70
Sierra Leone	2 567	320	12.5	71	26	1.01
Zaire	3 460	663	19.2	178	27	0.78
Total	10 300	1 583	15.4	420	73	0.71

[a] Tested by enzyme-linked immunosorbent assay with monkeypox antigen.
[b] Tested by enzyme-linked immunosorbent assay adsorption.

Follow-up visits by Dr Alexander Gromyko and Dr Jean-Paul Ryst to Côte d'Ivoire and Sierra Leone in June–July 1982 to examine those who had monkeypox virus antibody in their sera showed that some specimens had inadvertently been taken from vaccinated subjects. However, none of the 13 subjects investigated had unequivocal evidence of past vesiculo-pustular disease (by history or residual pockmarks). If any of them had been infected with monkeypox virus, as the serological results indicated, the infection was subclinical or so mild as to have been forgotten.

Because surveillance was much better in Zaire, it was possible to obtain more informa-

BY COURTESY OF Z. JEŽEK

Plate 29.8. Team leaders of special investigations in Kole, outside Kole hospital, Zaire, in 1981. *Left to right:* K.M. Paluku, M. Mutombo, Okwo-Bele, F.M. Meier, Z. Ježek.

tion about the possible frequency of subclinical infection from the survey in Kole Zone, in which Ježek was able to visit some 400 localities, involving about 10 000 households and about 50 000 persons, who were examined for vaccination scars and facial pockmarks (Ježek et al., 1987a). Only 15% of those investigated had no vaccination scar, and 1.3% of them had facial skin changes suggesting a past attack of a vesiculo-pustular disease. Of a total of 3460 serum samples collected from persons without vaccination scars, 27 showed evidence of the presence of monkeypox-virus-specific antibodies by the radioimmunoassay adsorption test. The subsequent field investigation of 19 of these subjects, who were less than 15 years old, revealed that 12 of them had experienced vesiculo-pustular disease or fever with lymphadenopathy in the past, 1 had a possible vaccination scar, and the remaining 6 had no signs or history of a disease like human monkeypox. The prevalence rate of monkeypox-virus-specific antibodies showed significant differences in different age groups; it was 4 times higher in the children aged 5–9 years (13.1 per 1000) than in those aged 0–4 years (3.3 per 1000).

As with serological surveys among wild animals in Zaire, the lack of a serological test that is sufficiently sensitive and specific to permit the diagnosis of a previous monkeypox virus infection without resorting to serum adsorption has made it impossible to determine the prevalence of human infections with monkeypox virus from the results of these 4 surveys. The significance of the overall orthopoxvirus-positive antibody rate of 15.4% remains obscure; it may have been due to antibodies to vaccinia virus or to a "non-specific reacting material" (J. H. Nakano, personal communication, 1986). However, follow-up studies in 3 countries support the view that emerged from intensive surveillance in Zaire (see Table 29.6)—namely, that some infections of unvaccinated humans with monkeypox virus are subclinical.

Ecological Studies

The epidemiology of primary cases of human monkeypox—i.e., those derived from an animal source—can be elucidated only from a knowledge of the ecology of the virus, involving the determination of which animals act as reservoir and incidental hosts and the way in which the virus is transmitted from one animal to another. Initially, studies of this problem were focused on monkeys. Serological surveys of Asian monkeys were negative, but monkeypox-virus-specific antibodies were found in several species of monkeys that occur in central and western Africa.

Because members of each species of monkey usually move in small self-contained troops, and because monkeypox virus does not cause persistent infections and is not transmitted by flying arthropods, it seems unlikely that non-human primates are the reservoir hosts of the virus. From 1979 onwards, therefore, attention was directed to a wider range of wild animals, especially terrestrial and arboreal rodents, some of which occur in populations that remain sufficiently large to support enzootic monkeypox virus infection.

Serological survey of captive African primates

Altogether 1447 sera of African primates held in various laboratories in Africa, Europe and the USA were tested for orthopoxvirus antibodies by either HI or neutralization tests; all were negative (Arita et al., 1972). With the possible exception of sera from 25 gorillas and 167 chimpanzees, all were obtained from animals captured in countries which have not reported cases of monkeypox, and the monkeys belonged to species occurring in the savanna rather than in tropical rain forests.

Serological surveys of primates from western Africa

Breman et al. (1977c) examined primate sera that had been collected in western Africa for a yellow fever survey. HI and neutralization tests were done on 206 sera obtained from 27 different sampling zones in Côte d'Ivoire, Mali and Upper Volta (now Burkina Faso), which were situated in forest and heavily wooded preforest and in the savanna. Out of 195 sera, 15 (8%) were orthopoxvirus-positive by HI and 44 (23%) by neutralization tests. The testing of 3 HI-positive sera from forest-dwelling monkeys (1 *Colobus badius* and 2 *Cercopithecus petaurista*) by immunofluorescence after adsorption showed that they contained monkeypox-virus-specific antibodies (Gispen et al., 1976).

In another survey, 692 sera obtained from a variety of animals from Chad, Côte d'Ivoire, Liberia, Nigeria, Senegal, Sierra Leone, and Upper Volta between 1970 and 1972 were tested (J. H. Nakano, unpublished observations, 1973). One hundred and fifty-eight (23%) gave positive results by the HI test and 50 out of 186 (27%) were positive by neutralization. Among sera from non-human primates included in the 692 samples, 92 out of 334 (28%) gave positive HI results; 35 out of 147 sera tested by neutralization (24%) gave positive results. Positive HI titres were observed with occasional serum samples obtained from a variety of other animals, including squirrels, rodents, ungulates, and wart-hogs. Subsequently, 273 of the monkey sera were tested by radioimmunoassay adsorption tests. Seven sera contained monkeypox-virus-specific antibodies: 2 from *Cercopithecus petaurista*, 2 from *Cercopithecus aethiops*, 2 from *Cercopithecus nictitans* and 1 from *Colobus badius* (J. H. Nakano, personal communication, 1986). The most interesting result was that obtained with *C. aethiops* from Côte d'Ivoire. Not only is this monkey typically an inhabitant of the savanna rather than the tropical rain forest, but it is the species that was exported from western Africa to North American and European countries on a large scale during the period when monkeypox was occurring in captive monkeys in these countries, and animals of this species may have been the source of infection of Asian monkeys during transit.

Tissues from 648 animals of 73 species obtained in Liberia and Nigeria in 1971 were tested for orthopoxviruses by 2 serial passages in primary monkey kidney cells with negative results (J. H. Nakano, personal communication, 1983).

Studies on material from Zaire, 1971–1979

Since most cases of human monkeypox had occurred in Zaire, attempts to determine the reservoir host or hosts of the virus were subsequently concentrated in that country, mostly in places in which human monkeypox cases had occurred.

Investigations by the WHO collaborating centre, Moscow. Between 1971 and 1975 serological and virological investigations concerning a wild-animal reservoir of monkeypox virus were carried out at the WHO collaborating centre in Moscow. Some 200 sera from areas distant from what is now recognized as the monkeypox enzootic area (see Fig. 29.2) were virtually all negative, whereas monkey sera from Zaire collected in 1971 and 1973 showed 14 out of 81 positive by the HI test and 11 out of 65 by the neutralization test (Marennikova et al., 1975). Subsequently another collection of sera from Zaire yielded

Table 29.11. Results of haemagglutination-inhibition, radioimmunoassay and radioimmunoassay adsorption tests on monkey and squirrel sera collected in Zaire in July 1979[a]

Species	Haemagglutination-inhibition test[b]		Radioimmunoassay test[b]		Monkeypox-virus-specific antibodies[c]	
	Number tested	Number positive	Number tested	Number positive	Number tested	Number positive[d]
Monkeys:						
Allenopithecus nigroviridis	10	7	10	8	8	7
Cercocebus albigena	3	0	3	0	0	–
Cercocebus galeritus	11	5	11	2	2	2
Cercopithecus ascanius	94	30	93	20	20	13
Cercopithecus mona	37	11	37	4	4	2
Cercopithecus neglectus	10	1	10	0	0	–
Cercopithecus nictitans	47	10	47	1	1	1
Cercopithecus pogonias	14	7	14	0	0	–
Colobus pennanti	10	3	7	0	0	–
Perdicticus potto	5	1	5	0	0	–
Squirrels:						
Funisciurus anerythrus and *F. isabella*	48	10	44	6	6	6
Heliosciurus rufobrachium	58	25	51	0	0	–

[a] Based on unpublished observations by J. H. Nakano.
[b] Using vaccinia virus antigens.
[c] By radioimmunoassay adsorption tests.
[d] Discrepancies between number tested and number positive due to non-specific reacting material.

24 HI-positive monkey sera out of 117 tested and 26 HI-positive rodent sera out of 245 tested.

Attempts were made to isolate virus on the chorioallantoic membrane from the kidneys of primates, rats, and squirrels collected in Zaire. None yielded monkeypox virus, but "whitepox" virus was said to have been obtained from 4 specimens and vaccinia virus from 1 specimen (see Chapter 30, Table 30.2).

Investigations by the WHO collaborating centre, Atlanta. In July 1979 a large-scale ecological survey in Zaire was organized by Dr Joel Breman, of the WHO Smallpox Eradication unit. Sera and organs were obtained from a wide variety of wild animals. The animal species were identified by expert zoologists and the sera and organs were tested at the WHO collaborating centre in Atlanta. In all, 1331 sera from 45 species of wild animals were tested by the HI test as a screening test for orthopoxvirus antibodies; 227 sera (17%), from a wide range of animals, gave positive results (J. H. Nakano, personal communications, 1983, 1986). All 50 sera from *Rattus* spp. were negative.

The subsequent testing of certain sera by radioimmunoassay adsorption tests cast doubt on the significance of the positive results obtained by the HI test, since none of 25 HI-positive sera of the squirrel *Heliosciurus rufobrachium* gave positive results by radioimmunoassay (Table 29.11). On the other hand, additional radioimmunoassay adsorption tests on monkey and squirrel sera from this collection revealed positive results in 5 species of monkey and in squirrels of the genus *Funisciurus* (J. H. Nakano, personal communication, 1986).

Kidneys and spleens from 930 of the animals from the 1979 Zaire study, including all the monkeys, were passaged in Vero cells, and the monkey material was also tested on the chorioallantoic membrane, with negative results (J. H. Nakano, personal communication, 1983).

Studies in Zaire, 1985–1986. Ecological investigations in Zaire were renewed in 1985, under the direction of Dr L. Khodakevich. Attention was concentrated on animals found around the houses and in the adjacent agricultural area near villages in which cases of human monkeypox had recently occurred. An early and exciting result was the recovery of monkeypox virus from a diseased squirrel (*Funisciurus anerythrus*) (Khodakevich et al., 1986). This species of squirrel is quite common in the agricultural areas adjoining villages, where it feeds on oil palm seeds.

Subsequent studies on sera from terrestrial rodents and goats found near houses and squirrels found in the agricultural area revealed many monkeypox-virus-specific sera in 2 species of squirrel (*Funisciurus anerythrus* and *Heliosciurus rufobrachium*), but none in the other animals (Table 29.12; Khodakevich et al., 1987b). Investigations into the significance of the squirrel, *Funisciurus anerythrus*, as a possible reservoir host of monkeypox virus are proceeding as this book goes to press.

Table 29.12. Results of haemagglutination-inhibition, radioimmunoassay and radioimmunoassay adsorption tests on sera from animals living in the settlements and agricultural areas adjacent to selected villages in Zaire, 1985–1986[a]

Species	Haemagglutination-inhibition test[b]		Radioimmunoassay test[b]		Monkeypox-virus-specific antibodies[c]	
	Number tested	Number positive	Number tested	Number positive	Number tested	Number positive[d]
Terrestrial rodents[e]	579	180[f]	579	0	0	-
Goats	121	0	121	0	0	-
Cats	65	11	65	4	4	0
Squirrels:						
Heliosciurus rufobrachium	39	8	39	7	7	7
Funisciurus anerythrus	332	41	337	92	83	80

[a] Based on unpublished observations by J.H. Nakano.
[b] Using vaccinia virus antigens.
[c] By radioimmunoassay adsorption tests.
[d] Discrepancies between number tested and number positive due to non-specific reacting material.
[e] Various species found near houses.
[f] Non-specific.

MONKEYPOX: THE OVERALL PICTURE

Laboratory studies show that monkeypox virus is a distinct species of *Orthopoxvirus*. First reported as the cause of epizootics among captive monkeys in laboratory colonies in Europe and the USA and in an epizootic in a zoological garden in the Netherlands, it was found in 1970 to be the causative agent of a generalized human infection that clinically resembled smallpox.

Unlike smallpox, however, human monkeypox occurs only in persons living in small villages in tropical rain forests in central and western Africa, where hunting is an important method of obtaining food. The vast majority of reported cases have been found in Zaire, during an intensive surveillance campaign based on health institutions that has been in operation there since late in 1981. The majority of cases can be attributed to infection from an animal source, but person-to-person infection sometimes occurs, mainly between unvaccinated children. The longest chain of transmission observed so far is an incident in which there appeared to be 4 serial person-to-person infections (Ježek et al. 1986a). It seems likely that any of several animal species (chimpanzee, several species of monkey, 2 species of squirrel, and perhaps other animals) may serve as the source of human infections.

Even in the parts of Zaire in which it appears to be the most common and is best reported, monkeypox is a rare disease (331 known cases in a population of about 5 million during the 5 years 1982–1986). However, serological studies suggest that occasionally subclinical infections occur among unvaccinated as well as vaccinated persons. There is no reason to believe that it is a new disease or that its frequency is increasing. Indeed, it appears to be disappearing from countries in western Africa, probably because of ecological changes associated with development.

OTHER ORTHOPOXVIRUS INFECTIONS OF MAN

As well as being the natural host of variola virus and an occasional, incidental host of monkeypox virus, man is susceptible to 2 other species of *Orthopoxvirus*, each of which has a broad host range: vaccinia and cowpox. Deliberate vaccination and accidental person-to-person infection with vaccinia virus have been described in Chapter 7. The present chapter is here concerned with human infections with vaccinia and cowpox viruses acquired from animals and with camelpox.

Vaccinia

General

Since vaccination was formerly practised on such a large scale and since vaccinia virus has a broad host range, it is not surprising that domestic animals were sometimes accidentally infected with the virus (Topciu et al., 1976). Human beings could, in turn, be infected from the lesions on domestic animals. Dekking (1964) found that in 36 virologically confirmed outbreaks of "cowpox" in cattle in the Netherlands, 28 were caused by cowpox virus and 8 by vaccinia virus. In the USSR, Maltseva et al. (1966) showed that each of 5 outbreaks of a pox disease affecting cattle and human beings between 1959 and 1963 was caused by vaccinia virus.

Outbreaks of Vaccinia in Cattle and Man

In 1964 an outbreak of pox infection occurred on a dairy farm in El Salvador in which 22 persons and 450 cows were affected (Lum et al., 1967). It was detected following the admission to hospital of 2 patients with pustular nodules on the hands. All except one of the human cases occurred in milkers; the exception was a woman who washed the towels used by the milkers to clean the cows' udders. Almost all the cows in the herd were infected before the epizootic ceased. The source of the infection was a milker who had been vaccinated on 18 August, had a severe primary reaction, and returned to work on 2 September. The first primary human case occurred 9 days later, presumably via lesions on a cow. Vaccinia virus was recovered from 5 human patients and 1 cow.

Buffalopox

Buffalopox, due to infection of buffaloes with vaccinia virus, was a relatively common disease in India and in other countries in which buffaloes are used for milk production (Lal & Singh, 1977). Usually lesions were confined to the teats of milking buffaloes, but sometimes generalized lesions occurred and calves got lesions on the face and mouth which interfered with their ability to suck. Human infections, usually comprising small lesions on the hands or forearms of milkers, occurred in most outbreaks and acted as the principal mode of transfer of the virus from one buffalo cow to another. The vaccination of milkers was positively incriminated as the source of one outbreak in the USSR (Ganiev & Farzaliev, 1964) and all other outbreaks have occurred in situations in which the infection of the buffaloes could have originated from vaccinated human beings. The causative agent was identified as vaccinia virus in most outbreaks. Baxby & Hill (1971) categorized 1 isolate as a separate species—"buffalopox virus"—on the basis of its biological characteristics, notably a ceiling temperature of 38.5 °C compared with 41 °C for vaccinia virus and the production of smaller pocks on the chorioallantoic membrane and smaller plaques in RK 13 cells. However, analysis of the DNA of this isolate indicates that it is also a strain of vaccinia virus (K. R. Dumbell, personal communication, 1982).

It was assumed that buffalopox would cease to occur after the cessation of routine vaccination in 1979–1980, but outbreaks continue to be reported in Maharashtra State and other parts of India. Analysis of the DNA of viruses recovered from lesions in buffaloes shows that they are strains of vaccinia virus (K. R. Dumbell, personal communication, 1986). These outbreaks do not appear to have been associated with human vaccination; studies on their epidemiology are in progress as this book goes to press.

Cowpox

History and geographical distribution

The history of cowpox in relation to the origins of Jennerian vaccination has been described in Chapters 2 and 6. It was not until 1939 that Downie (1939a,b) clearly differentiated cowpox virus from vaccinia virus. Classical cowpox has not been described outside of Europe, but strains of cowpox virus have been recovered from rodents in Turkmenia (USSR).

Epidemiology

The traditional mode of infection of human beings with cowpox virus was by "inoculation" of the hands of milkers by contact with ulcers on the teats of cattle caused by cowpox virus (see Plate 29.6 A and 29.6 D). This was undoubtedly the usual

Table 29.13. Features of 16 virologically confirmed cases of infection of humans with cowpox virus in England[a]

Outbreak		Contact with infected cows	Human cases		
Place	Year		Farm worker[b]	Age	Lesions
Dorchester	1969	+	+	Adult	Hand
Winchester	1969	–	–	Adult	Hand
Middlesbrough	1971	–	–	8 years	Chin
Exeter	1971	+	+	Adult	Hand
Burnley	1974	–	–	14 years	Hand, chin
Penrith	1974	–	–	Adult	Hand
Scarborough	1975	–	–	6 years	Face
Lincoln	1975	–	–	17 years	Hand
Bristol	1976	–	–	17 years	Face
Taunton	1976	+	+	Adult	Hand
Leeds	1978	–	–	Adult	Hand
Newcastle	1978	–	–	Adult	Hand
Shrewsbury	1978	–	–	11 years	Hand
Taunton	1978	–	–	Adult	Hand
Stoke	1979	–	+	Adult	?
Norwich	1981	–	–	9 years	Hand

[a] From Baxby (1977a); D. Baxby, personal communication, 1983.
[b] Occupations of the other patients were diverse.

mode of infection and over the years many such episodes have been reported. Human cowpox was regarded as a rare zoonosis, contracted by the direct contact of milkers with lesions on the teats of cows and resulting in an ulcer or ulcers that remained localized at the inoculation site (Downie, 1951, 1965a; Dekking, 1964).

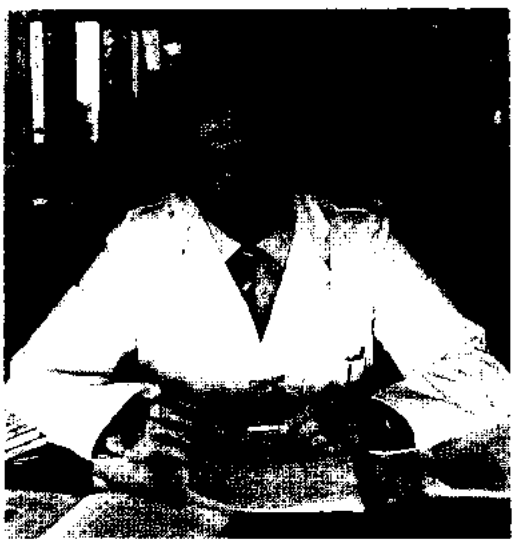

Plate 29.9. Derrick Baxby (b. 1940), British authority on orthopoxviruses, with a particular interest in cowpox and the history of vaccination.

Bovine cowpox is not a common disease (Gibbs et al., 1973) and apparently never was, even in Jenner's time, and the occurrence of lesions of "spurious cowpox" on cows' teats (see below) gave rise to much confusion when such lesions were used as a source of vaccine. Ceely (1842), who provided one of the best and most detailed descriptions of cowpox in bovines, noted that: "The disease is occasionally epizootic . . . more commonly sporadic or nearly solitary. It may be seen sometimes at several contiguous farms, at other times one or two farms entirely escape its visitation. Many years may elapse before it recurs at a given farm or vicinity, although all the animals may have been changed in the meantime."

Baxby (1977a; personal communication, 1983) has pointed out that cows were directly implicated as a source of cowpox virus in only 3 out of 16 virologically confirmed cases in human beings in England between 1969 and 1981 (Table 29.13). No source of infection could be discovered for the other 13 cases. Only 4 of the cases occurred in farm workers. Other studies (review: Baxby et al., 1979) have shown that cowpox virus (defining the species according to the biological characteristics described in Chapter 2, Table 2.3) has caused sporadic infections in domestic cats, large felines, elephants, okapis and a rhinoceros (Table 29.14), none of these infections

Table 29.14. Animals from which cowpox virus has been recovered

Animal	Disease		Place	Reference
	Form	Degree of severity		
Man	Lesions on hands	Mild	England	Davies et al., 1938
Cow	Lesions on teats	Mild	England	Dekking, 1964
Okapi	Generalized rash	Moderate	Rotterdam Zoo	Zwart et al., 1971
Elephant	Generalized rash	Moderate	Federal Republic of Germany (circus)	Gehring et al., 1972; Baxby & Ghaboosi, 1977
Rhinoceros	Generalized rash	Moderate	Münster Zoo	Schaller & Pilaski, 1979
Lion	Pulmonary	Severe	Moscow Zoo	Marennikova et al., 1977
Cheetah	Pulmonary	Severe		
Black panther	Pulmonary	Severe		
Black panther	Generalized rash	Mild		
Ocelot	Generalized rash	Severe		
Jaguar	Generalized rash	Mild		
Puma	Generalized rash	Mild		
Anteater	Hemorrhagic rash	Severe		
Far Eastern cat	Generalized rash	Mild		
Cheetah	Pulmonary	Severe	Whipsnade Zoo	Baxby et al., 1982
	Generalized rash	Severe		
Domestic cat	Multiple skin lesions	Mild	England	Bennett et al., 1986
			Austria	Schönbauer et al., 1982
White rat	Pulmonary	Severe	Moscow Zoo	Marennikova et al., 1978a
	Generalized rash			
Norway rat	Generalized rash	Mild	USSR	Malboroda, 1982
Great gerbil, Yellow susilk	Normal animals captured in wild	Nil	Turkmenia, USSR	Marennikova et al., 1978b
		Nil		

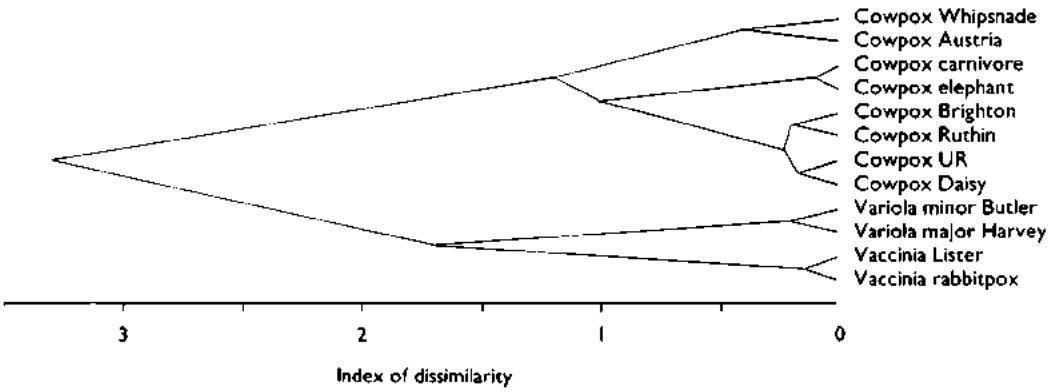

Fig. 29.4. Dendrogram illustrating the similarities and differences between *HindIII*, *XhoI* and *SmoI* cleavage sites on the DNAs of 8 strains of cowpox virus, 2 strains of variola virus and 2 strains of vaccinia virus. Analysis as for Fig. 29.1. Number of attributes = 70. (Data from Mackett, 1981.)

having originated from contact with cases of bovine or human cowpox. The validity of the species diagnosis is supported by analyses of the DNA obtained from several of these isolates (Fig. 29.4). All could be clearly differentiated from vaccinia and variola DNA. The dissimilarities between different strains of cowpox DNA relate in a general way to their geographical origins, and strains from unusual hosts (elephants and large felines) clearly have cowpox virus DNA.

Man, cows and the other animals listed in Table 29.14 are probably all incidental hosts of cowpox virus, of no importance as far as its perpetutation in nature is concerned. The recovery of cowpox virus from wild rodents in Turkmenia (Ladnyj et al., 1975; Marennikova et al., 1978b; Plate 29.10) and the demonstration that a substantial number of them were serologically positive (Table 29.15) suggests that susliks and gerbils might be natural reservoir hosts of cowpox virus in Turkmenia. These animals do not occur in the United Kingdom, but Kaplan et al. (1980), in a study of virus infections in small British field rodents, demonstrated orthopoxvirus antibodies in wild voles; these could be due to cowpox virus. It is not unreasonable to suppose that cowpox virus, which has a wide host range, produces enzootic infections in a variety of rodents, from which it is occasionally transferred to other animals: cows, cats, zoo animals (possibly via domestic rats used as feed, as in the Moscow Zoo outbreak; Marennikova & Shelukhina, 1976) and sometimes man (Baxby, 1977a, 1982b). In turn, cows, cats and sometimes zoo animals (Marennikova et al., 1977) could serve as the source of infection for humans.

Differential diagnosis of lesions on cows' teats

Jenner recognized that not all ulcers on the teats of dairy cows were caused by "variolae

Table 29.15. Evidence of cowpox virus infection in white rats in Moscow and in wild rodents in Turkmenia[a]

Species	Serological test (captured animals)		Virus isolation		
	Haemagglutination inhibition[b]	Neutralization[b,c]	Number[b,c]	Organs	Clinical condition
White rat (zoo)	12/31	..	..		
White rat (breeding colony)	33/100	..	4/100	Lungs and kidneys	Sick
				Lungs	Healthy
Great gerbil (*Rhobomys opimus*)	57/306	43/258	2/1102	Kidneys, spleen	Healthy
Large-toothed suslik (*Citellus fulvus*)	25/163	9/103	1/173	Kidneys	Healthy
Midday gerbil (*Meriones meridianus*)	2/35	2/35	0/133	–	Healthy
Meriones erythrourus	1/32	1/32	0/184	–	Healthy

[a] Based on Ladnyj et al. (1975); Marennikova et al. (1978b).
[b] Number positive/number tested.
[c] .. = data not recorded.

Plate 29.10. Reservoir hosts of cowpox virus in Turkmenia. **A**: Yellow suslik (*Citellus fulvus*). **B**: Great gerbil (*Rhombomys opimus*).

Plate 29.11. Camelpox in camels in Somalia. **A**: Thick brown crusts around the mouth and lesions on the tongue. **B**: Generalized lesions.

vaccinae", so that material taken from such lesions sometimes lacked the capacity to protect humans against smallpox; he termed such lesions "spurious cowpox" (Jenner, 1799). In addition to cowpox and vaccinia virus, 2 other viruses can cause ulcers on the teats of cows (Gibbs et al., 1970; Baxby, 1981). These are bovine herpes mammillitis virus and pseudocowpox virus (Plate 29.6 B). Both are enzootic diseases of bovines, and are much more common than cowpox virus infections in dairy herds. Pseudocowpox virus is transmissible to man, to produce milker's nodules (see below).

Clinical features of cowpox in man

Downie (1965a) has described the lesions found in humans infected with cowpox virus (Plate 29.6 D) as follows. One or more lesions usually appear on the hands—the thumbs, the first interdigital cleft and the forefinger being especially liable to attack. Scratches or abrasions of the skin may determine the localization of the lesions elsewhere on the hands, forearms or face. The lesions resemble those of primary vaccination, passing through the stages of vesicle and pustule before a scab forms. Local oedema is usually more pronounced than in vaccination and there is lymphangitis, lymphadenitis and often fever for a few days. Baxby (1977a) noted that cowpox in children was occasionally rather severe. However, although multiple primary lesions sometimes occur, a generalized rash has not been reported, but one case of post-cowpox encephalitis has been described (Verlinde, 1951).

Camelpox

Camelpox is a common disease of dromedary camels. The original report identifying camelpox virus as an orthopoxvirus (Baxby, 1972) caused some concern to those involved in the global smallpox eradication campaign since it was entitled "Smallpox-like viruses from camels in Iran". However, subsequent investigations (see Chapter 2) showed that it was caused by a distinct species of *Orthopoxvirus* that has a narrow host range. Among camels, skin lesions occur mainly on the head, neck and forelegs, or all over the body. Young animals, in particular, may suffer a severe disease which is sometimes fatal (Plate 29.11). Camelpox is enzootic in Somalia (Ježek et al., 1983) and in most other areas in which camels are common (Egypt, India, the Islamic Republic of Iran, Iraq, Kenya and the USSR) but not among feral camels in Australia.

Although there were occasional reports in the older literature that camel drivers could contract local lesions on the hands and arms from contact with affected animals, the experience during the global smallpox eradication programme, especially in Somalia, suggested that human camelpox rarely if ever occurred. Kříž (1982) described a possible case in a 40-year-old unvaccinated Somali man who was a member of a nomadic group among whose camels there was a severe epizootic of camelpox. There were 3 lesions on the left arm and 1 on the right, which went through vesicular and pustular stages before scabbing. It was not possible to obtain lesion material for laboratory confirmation, but the serum from this patient gave a positive orthopoxvirus HI test. A survey among 286 camel herdsmen in the area, only one-third of whom had been vaccinated, revealed only 2 other cases of skin lesions, both diagnosed as tropical ulcers. A subsequent survey of another 179 herdsmen handling affected camels, 12% of whom had been vaccinated, revealed few skin eruptions, none of which yielded a poxvirus (Ježek et al., 1983). Out of a total of 335 specimens taken from the skin lesions of persons who might have come into contact with diseased camels, none was positive for poxvirus particles, and inquiries among some 20 000 persons at risk yielded only 1 possible case of human camelpox, that reported by Kříž (1982).

PARAPOXVIRUS INFECTIONS

A number of domestic animals—sheep, goats, cattle, and camels—sustain infections with different strains or species of the genus *Parapoxvirus*. The lesions in each species of animal usually take the form either of scattered papules and nodules in the skin or of a papular stomatitis, with lesions on the lips and gums ("scabby mouth" of sheep; bovine papular stomatitis). One strain of parapoxvirus is spread among cows and produces ulcerative lesions on the teats (Plate 29.6 B), which are called pseudocowpox and constitute one of the forms of the "spurious cowpox" of Jenner (Gibbs & Osborne, 1974). Calves sucking from dams with pseudocowpox usually get lesions on the mouth and

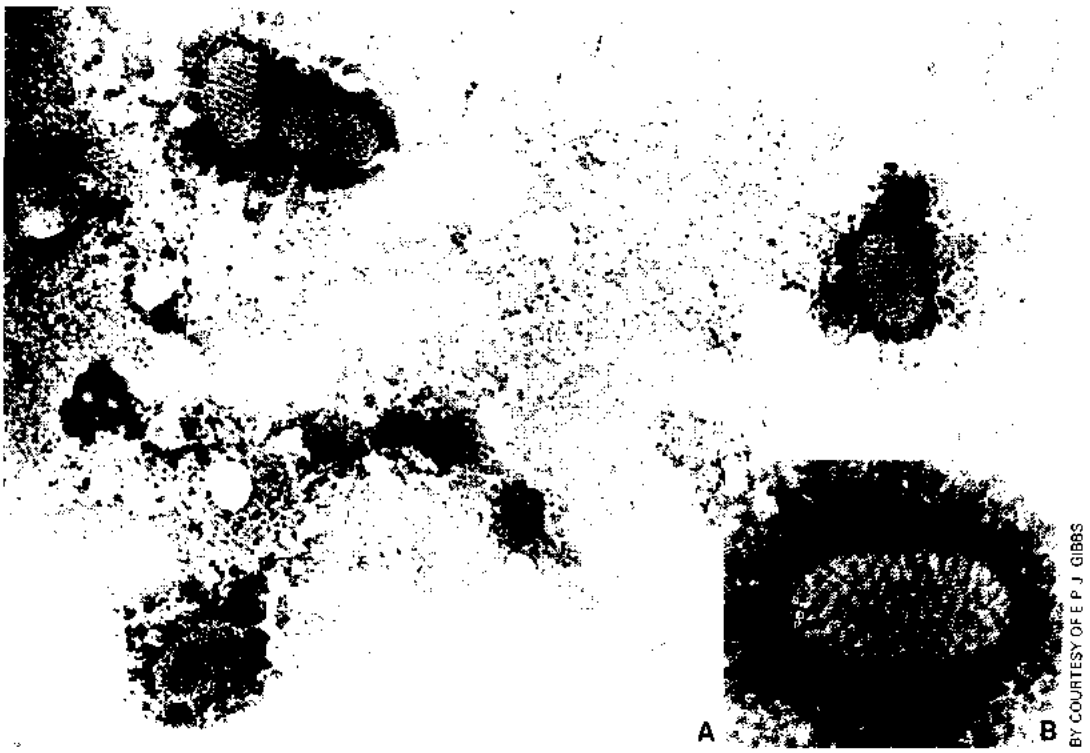

Plate 29.12. **A:** Virions of the parapoxvirus of pseudocowpox, which produces lesions of milker's nodules in humans. **B:** Virion at higher magnification, showing the regular spiral structure of the tubule of the outer coat, which is characteristic of the genus *Parapoxvirus*.

lips. Bovine papular stomatitis is caused by a different species of parapoxvirus and is found more commonly in beef than in dairy cattle (Tripathy et al., 1981). Five out of 57 cases of "camelpox" in Somalia that were investigated virologically in 1978–1979 were caused by a parapoxvirus (J. H. Nakano, personal communication, 1986).

Humans can be infected accidentally with these parapoxviruses through abrasions of the skin. The disease acquired from sheep or goats is termed orf (review: Johannessen et al., 1975); that acquired by milkers from the ulcers on the teats of cattle is called milker's nodules. The lesions in cattle and sheep often ulcerate; milker's nodules in humans are usually small indolent papules (Plate 29.6 E). Human orf is associated with umbilicated proliferative lesions that often ulcerate before healing (Plate 29.6 F).

All parapoxviruses have an identical morphology, which is quite distinctive (Plate 29.12), the virions being smaller than those of the orthopoxviruses and having a regular surface structure.

Parapoxvirus infections are of some importance in the consideration of smallpox for two rather trivial reasons: the lesions on cows' teats constituted an early source of confusion with genuine cowpox, and the particles found in scrapings of human lesions reported by electron microscopists simply as "poxvirus particles" might unnecessarily alarm public health authorities.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a specifically human skin disease caused by a poxvirus which has not yet been cultivated or transmitted to laboratory animals (review: Postlethwaite, 1970). The lesions are pearly, flesh-coloured, raised, firm, umbilicated skin nodules, 2–5 mm in diameter, which may appear anywhere on the body except the palms and soles. The nodules are painless and at the top of each there is often an opening through which a small white core can be seen. There are no constitutional disturbances. The le-

sions may persist for months or even a few years before resolving spontaneously.

Molluscum contagiosum has a world-wide distribution. In some places—e.g., Papua New Guinea (Sturt et al., 1971) and Zaire—it is very common in children. It may occur sporadically or in small epidemics. Direct or indirect contagion appears to be the mode of spread and in western countries public baths and swimming-pools may be implicated. Among young adults it may be a sexually transmitted disease (Brown et al., 1981).

In negatively stained preparations the virions are morphologically very like those of vaccinia virus, although Nakano (1985) noted that the surface tubules were more prominent. However, since the lesions are so distinctive, and since the virus cannot be cultivated, molluscum contagiosum was not regarded as a serious source of confusion in the global smallpox eradication campaign.

TANAPOX VIRUS INFECTIONS

Tanapox was first observed as an acute febrile illness, associated with localized nodular skin lesions and caused by a poxvirus, which occurred in epidemics in 1957 and 1962 among people living in the flood plain of the Tana river in Kenya (Downie et al., 1971). Serological studies (Manson-Bahr & Downie, 1973) showed that it was endemic in this area, and subsequently many cases were seen during surveillance for monkeypox in Zaire in 1977–1984 (Ježek et al., 1985). The same virus (Downie & España, 1972) gave rise to epizootic infection in rhesus monkeys in 3 primate centres in the USA in 1966; in each of these outbreaks some of the animal handlers were infected, apparently through skin abrasions (Nakano, 1978).

Ježek et al. (1985) have published a detailed analysis of the clinical and epidemiological features of tanapox as seen in 264 cases in Zaire in which the diagnosis was confirmed by electron microscopy. The incubation period in natural human cases is unknown, but in a person infected by the intradermal inoculation of about 10^4 infectious particles (as assayed in tissue culture), erythema and central thickening appeared by the 4th day (Downie et al., 1971). Most patients have a mild pre-eruptive fever, sometimes accompanied by severe headache and backache and often with itching at the site of the eventual skin lesion.

The appearance and evolution of the characteristic skin lesions are illustrated in Plate 29.7. Initially there is a small nodule, without the central abrasion that is often seen with an insect bite. The nodule soon becomes papular and gradually enlarges to reach a maximum diameter of about 15 mm by the end of the second week. It is surrounded by an oedematous zone and a large erythematous areola. The draining lymph nodes are enlarged and tender from about the 5th day after the appearance of the skin lesion, which may remain nodular but usually ulcerates during the third week and then gradually heals within 5–6 weeks, leaving a scar. In Kenya, Downie et al. (1971) noted that the lesions were almost always solitary and on the face, neck, upper arm and trunk. In Zaire, however, Ježek et al. (1985) noted that 22% of patients had multiple lesions—usually 2 but sometimes 3 or more, the maximum number seen on one patient being 10. Multiple lesions were often close together and usually evolved simultaneously, although they differed in size. In Zaire the distribution of lesions was different from that seen in Kenya, 72% being on the lower limbs, 17% on the upper limbs, 7% on the trunk and 5% on the head.

Especially if there were multiple lesions, a case of tanapox could initially be mistaken for human monkeypox (or in former times smallpox), perhaps modified because of vaccination, but the slow evolution and lack of pustulation clearly differentiate tanapox from any of the orthopoxvirus infections. The clinical diagnosis can be confirmed by the demonstration with the electron microscope of poxviruses which have a characteristic envelope (Plate 29.13) and fail to grow on the chorioallantoic membrane (Nakano, 1985).

Some strains of tanapox virus grow in cultures of monkey or human cells, producing focal lesions characterized by intense granularity followed by rounding up of the cells. Monkeys, but no other laboratory animals, are susceptible to experimental infection.

Human tanapox has been recognized in Kenya and Zaire, but probably occurs much more widely throughout tropical Africa. In Kenya, Downie et al. (1971) noted that epidemics in 1957 and 1963 were associated with periods of extensive flooding. In Zaire, cases occurred throughout the year but mainly in the period between November and

BY COURTESY OF J-H NAKANO

Plate 29.13. Virions of tanapox virus, as seen in negatively stained scrapings from a lesion. Most virions appear to have an envelope.

March (Ježek et al., 1985). The majority of cases seen in Zaire were found in the township of Lisala, among persons living within 300 metres of the Zaire river. Both sexes and all age groups were affected, and cases occurred much more frequently among persons who worked or played close to the river than among those engaged in hunting or working as plantation farmers. Although clusters of cases occurred both temporally and spatially, there was no indication that person-to-person spread occurred. Tanapox appears to be a zoonosis, but neither the reservoir host nor the mode of transmission from wild animals to man is known. Manson-Bahr & Downie (1973) suggested that tanapox virus may be transferred from monkeys or some other reservoir host to man by biting arthropods, possibly acting as mechanical vectors. Infection by mechanical transmission has been described among animal attendants (McNulty et al., 1968).

GENERAL COMMENT

Man is susceptible to a range of poxvirus infections, but only two of these, smallpox and human monkeypox, regularly produce an acute systemic infection with a generalized rash. Human monkeypox can be distinguished from smallpox only by the cultivation of the virus or the performance of a virus-specific serological test with convalescent serum, but the epidemiology of the two infections is quite different. Monkeypox was the only poxvirus infection other than smallpox seen during the eradication programme that gave rise to serious concern. However, the studies in Zaire described in this chapter provide good evidence that it is a rare zoonosis which cannot be sustained indefinitely by serial transmission in man.

Because vaccination can greatly modify the response of humans to either variola or monkeypox virus, so that if skin lesions do occur, they are very few or perhaps only a solitary one develops, other poxvirus infections sometimes cause problems in the differential diagnosis of smallpox or monkeypox, especially because electron microscopic examination of lesion material might reveal poxvirus particles.

The diagnosis of cowpox and vaccinia infections depends on the cultivation of the virus on the chorioallantoic membrane; that of tanapox on the clinical picture, the appearance of the virion in the electron microscope and its failure to grow on the chorioallantoic membrane. The lack of systemic symptoms and the characteristic chronic nodular skin lesions distinguish molluscum contagiosum from all other poxvirus diseases. The viruses of orf and milker's nodules can readily be distinguished by the characteristic morphology of the virion, as well as by serological tests.

When they were first studied in the laboratory, camelpox virus (Baxby, 1972) and taterapox virus (Lourie et al., 1975) were regarded with considerable suspicion because the pocks they produced on the chorioallantoic membrane very closely resembled those produced by variola virus. It is possible that similar causes of concern may arise, perhaps with orthopoxviruses of wild animals that have yet to be discovered. Comparison of their DNA with that of variola and monkeypox viruses should allow the proper categorization of any such isolates.

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CHAPTER 30

POTENTIAL SOURCES FOR A RETURN OF SMALLPOX

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INTRODUCTION

The eradication of smallpox was defined by successive WHO expert groups (WHO Scientific Group on Smallpox Eradication, 1968; WHO Expert Committee on Smallpox Eradication, 1972) as "the elimination of clinical illness caused by variola virus". An important corollary of this definition was that it did not involve the extinction of variola virus, as some experts had urged. The procedures for the certification of smallpox eradication described in Chapter 24 were therefore designed to ensure that no human cases had occurred in the countries concerned for at least 2 years—i.e., that the human-to-human chains of transmission of smallpox had been interrupted. Careful follow-up of rumours of suspected smallpox by national authorities and by WHO, described in Chapter 28, has failed to confirm a single case of smallpox in a field situation since the last case was recognized in Somalia in October 1977, although there were 2 laboratory-associated cases in Birmingham, England, in August–September 1978. The correctness of the conclusions that the Global Commission for the Certification of Smallpox Eradication arrived at in its deliberations in December 1979 (World Health Organization, 1980) has been borne out by 10 additional years of freedom from the disease.

As the expert groups which defined eradication recognized, the absence of cases of smallpox is not synonymous with the extinction of variola virus, and if the virus is

not extinct it is possible that further cases of smallpox could occur. This chapter is concerned with the known and hypothetical ways in which variola virus could be preserved and enter again into chains of human-to-human transmission. By far the most important, because it would be the most difficult to eliminate or circumvent, would be the continuing transmission of the virus in some wildlife reservoir or reservoirs. Indeed, such a situation would have made the permanent global eradication of smallpox an impossibility. This was therefore a matter that greatly exercised the staff of the WHO Smallpox Eradication unit from the outset of the global eradication programme (see Chapters 10 and 29). The lack of evidence of infection of humans from an animal host in Europe, North America and Australia, in which the disease no longer occurred, did not exclude this possibility for parts of Africa and Asia in which smallpox was still endemic until the 1970s. Although there was no documented evidence that this had taken place, it was conceivable that infection of man from an animal source might have occurred in the past without having been detected, as indeed proved to be the case with human monkeypox. Because of the reported isolations in laboratories in Bilthoven (Netherlands) and Moscow (USSR) of variola-like viruses ("whitepox" viruses) from animal tissues (see later in this chapter), investigation of this possibility remained a major concern of virologists involved in research associated with the eradication programme throughout the 1970s and into the early 1980s.

Material stored by variolators was another potential source for the recurrence of cases of smallpox which concerned the WHO Secretariat and members of the Global Commission, especially in countries such as Afghanistan in which low temperatures prevailed for much of the year. However, the most obvious source of virus that might cause human infection at some time in the future consists of laboratory stocks of variola virus, from which, indeed, the last known outbreak in the world originated (see Chapter 23). These could be stocks of virus known by WHO to be held in microbiologically secure laboratories, or they could be specimens in the deep-freeze storage facilities of any laboratory that had ever worked with the virus. Finally, stocks of virus may be held secretly, for possible use in microbiological warfare.

Other hypothetical sources of smallpox could be from virus released by reactivation in a human subject who had had the infection, or release of viable virus long preserved in scabs, on old clothes, or even in coffins. For the sake of completeness the possibility that another species of *Orthopoxvirus* might be "transformed" into variola virus (already discussed in Chapter 2) needs to be briefly reconsidered here, as a possible source for the return of smallpox.

IS THERE AN ANIMAL RESERVOIR OF VARIOLA VIRUS?

The presence of an animal reservoir of variola virus is in theory the most important potential source for a return of smallpox. In discussing the origin of variola virus in Chapter 2, we suggested that conditions suitable for its perpetuation as a specifically human pathogen have existed for a few thousand years at the most. Variola virus was therefore probably derived from some closely related orthopoxvirus that survived in nature by circulation in an animal that occurred in large numbers at the time of early man and had a much shorter life-span. In this chapter two possibilities will be discussed: that there is an animal reservoir of variola virus as we know it, or that some other animal orthopoxvirus could be "transformed" into variola virus by a few mutational steps or perhaps by chance recombination with another animal orthopoxvirus. The great importance of this question, from the point of view of smallpox eradication, can be illustrated by reconsidering briefly the history of the first deliberate attempt to eradicate a human disease, yellow fever, which has already been mentioned in another context in Chapter 9.

The Example of Yellow Fever

In 1915 the International Health Commission of the newly established Rockefeller Foundation agreed to help with the global eradication of yellow fever, an undertaking that General W. C. Gorgas, Surgeon-General of the United States Army and the hero of disease control during the construction of the Panama Canal, considered eminently feasible. Yellow fever was regarded as an urban disease, and its global eradication was based on a simple epidemiological concept:

"...that the disease could be acquired only through the bite of an *A. aegypti* mosquito that had become infected by feeding on a human being sick with yellow fever; that there were certain endemic centers of the disease that served as seedbeds; that these foci of infection were few in number, and that if they were destroyed, yellow fever would disappear forever." (Warren, 1951.)

It is a matter of history that this concept was too simple. As early as 1907 Franco et al. (1911) had recognized the existence in Colombia of another epidemiological situation—the contracting of yellow fever in the forest, rather than in urban areas. Another outbreak of yellow fever occurred in the same locality in 1916, but since *Aedes aegypti* could not be found there, it was assumed by the Gorgas Commission that the diagnosis was erroneous (Gorgas, 1917). Eventually Soper (1935, 1936) drew attention again to the paper of Franco et al. and described what he called "jungle yellow fever", which he postulated could be due to maintenance of the virus in another vertebrate host or perhaps long persistence in an invertebrate vector. At about the same time surveys of forest monkeys of many species in both Africa and South America revealed the presence of neutralizing antibodies in their sera. With the discovery of a vertebrate reservoir other than man, it was clear that the global eradication of yellow fever was impossible, although urban yellow fever could be eliminated by ridding towns and cities of *Aedes aegypti*.

The significance of the yellow fever experience was not lost on those who contemplated the global eradication of smallpox and investigations into the possibility that there might be an animal reservoir of variola virus in Africa or Asia were initiated soon after the Intensified Smallpox Eradication Programme was launched (see Chapter 10).

Smallpox in Apes and Monkeys

Experimental observations with variola virus had demonstrated that, unlike vaccinia and cowpox viruses, both of which have a wide host range, few laboratory animals could be infected with variola virus, except under unusual conditions (see Chapter 2). However, it had been demonstrated during the latter part of the 19th century that monkeys (probably *Macaca mulatta*) could be infected with variola virus (Zuelzer, 1874; Copeman, 1894), and later studies (Hahon, 1961) showed that many species of monkeys and apes were susceptible. Noble (1970) found that 3 species of New World monkeys that he tested were insusceptible to variola minor virus, although they reacted serologically but without symptoms to experimental infection with variola major virus.

Reported infections of primates in nature

Arita & Henderson (1968) reviewed the published accounts of supposed smallpox in primates as well as other naturally occurring epidemics of "pox" infections among monkey populations. Only 8 such episodes are known and only 4 of these occurred during the present century (Table 30.1). In only 2 instances was laboratory confirmation available; in each of these there had been close association between the primate concerned and cases of human smallpox.

"Smallpox" infection in a monkey population in the forests of southern Brazil was reported by Bleyer (1922), who noted that carcasses of *Mycetes seniculus* and *Cebus capucinus* were found under the trees, the dead animals having fallen from the tree-tops. Sick as well as dead monkeys were covered with numerous pustules like those seen in human smallpox and the mortality was extremely

Table 30.1 Episodes of presumed or proved naturally occurring "pox" infection in non-human primates

Country	Year	Species	Author
France	1767	?	Barrier, quoted by Schmidt (1870)
Panama	1841	?	Anderson (1861)
France	1842	?	Rayer, quoted by Schmidt (1870)
Trinidad	1858	?	Furlong, quoted by Schmidt (1870)
Brazil	1922	*Mycetes seniculus* *Cebus capucinus*	Bleyer (1922)
India	1936	*Macaca mulatta*	Rahman (quoted by Arita & Henderson, 1968)
Indonesia	1949	Orang-utan[a]	Gispen (1949)
India	1966	*Macaca mulatta*[b]	Mack & Noble (1970)

[a] Variola virus isolated.
[b] Serological and epidemiological evidence suggesting infection with variola virus.

high in certain districts. Anderson (1861) reported that a "smallpox" outbreak observed in 1841 in monkeys was followed by a smallpox outbreak in a human population in Panama. Two monkeys that he examined were covered with "perfectly formed" pustules. Schmidt (1870) mentioned 3 other episodes, 2 in France and 1 in Trinidad.

An outbreak of a vesiculo-pustular disease was observed by M. A. Rahman (quoted by Arita & Henderson, 1968) in rhesus monkeys in Bengal, India, in 1936. Many deaths were observed among monkeys which lived in mango groves near the town and visited the town frequently in search of food and water. The sick monkeys were quiet and lethargic and had pustular lesions, particularly on the face, palms and soles. When they died they fell from the trees and roof tops, and the carcasses were disposed of without any particular precautions being taken. Despite the poor vaccinial immunity status of the population, no human pox-like illnesses were observed.

All these episodes must be regarded with caution so far as their significance as evidence of an animal reservoir of variola virus is concerned. They may have been instances of the infection of primates from human cases of smallpox or they may have not been due to variola virus or indeed to any kind of poxvirus. However, 2 episodes have been well documented which demonstrate that primates in close contact with smallpox-infected humans may have become infected with variola virus. Gispen (1949) observed 2 orang-utans in the Jakarta Zoo which contracted a pox infection at the time of a smallpox epidemic in the area. Both animals were in the same cage and demonstrated typical lesions on the face, hands, and soles of the feet; Bras (1952a) performed an autopsy on the one that died (Plate 30.1). Variola virus was isolated on the chorioallantoic membrane of the chick embryo from specimens taken from both affected animals. Other monkeys in the zoo, none of which had been previously vaccinated, remained unaffected. The other episode occurred in India, where Mack & Noble (1970) recorded an unusual situation in which 1 or possibly 2 performing monkeys (*Macaca mulatta*) appear to have been infected with variola virus by intimate household contact with human cases of smallpox.

Throughout the global smallpox eradication campaign attempts were made to identify the source of infection in all outbreaks,

Plate 30.1. Orang-utan (*Pongo pygmaeus*) in the Jakarta Zoo, which was infected during the 1949 epidemic of smallpox and died.

and as the incidence of smallpox fell to low levels in each endemic country, this became a matter of high priority, so that chains of transmission could be traced. Thousands of such outbreaks in Africa and south-eastern Asia were investigated by skilled epidemiologists. In the vast majority, infection could be traced to a case of smallpox. Very rarely fomites (e.g., laundry items or burial shrouds) were implicated. In a few instances it was not possible to determine the source of the outbreaks. Some of them may have been due to infection acquired from mild unrecognized cases, or the source remained undetected through faulty or incomplete investigation. But the possibility of infection from an animal source was always present in the minds of epidemiologists in the rare instances in which no human source could be clearly identified. Never during the global smallpox eradication campaign could smallpox be traced back to an animal source. Finally, although monkeys are common in many of the countries of Africa and Asia in which smallpox was once endemic, sometimes living in close contact with man or

captured by hunters, no case of smallpox has been found in any of these countries since eradication.

Experimental transmission of smallpox between primates

More significant than isolated examples of smallpox in monkeys or the infection of animals by inoculation are 2 sets of observations on the natural transmission of variola virus from one primate to another. Noble & Rich (1969) showed that serial infection could be maintained for as many as 6 successive passages in *Macaca irus* (cynomolgus) monkeys placed in contact with other monkeys during the period of rash, but transmission then failed (Fig. 30.1). Among chimpanzees, Kalter et al. (1979) observed that 2 animals situated in cages near a chimpanzee experimentally inoculated with variola virus contracted smallpox, one suffering a severe illness. One other animal in the group escaped infection. Clearly, primates of several species are susceptible to variola virus, get a rash when infected, and can transmit the disease to other primates in contact with them. However, in *Macaca irus*, the only primate in which adequate studies were conducted, the infection persisted with some difficulty and then died out.

As was discussed in Chapter 2, smallpox could not be maintained in isolated human populations numbering under 200 000. Unless smallpox in non-human primates produced a situation in which recurrent infectivity could occur years after the primary infection, it is likely that populations of any particular species of monkey would be too small to maintain the disease. This is certainly true of chimpanzees and orang-utans, in which infection with variola virus causes a severe disease not unlike smallpox in man.

Monkeypox

It had been known since 1958 that monkeys in laboratory colonies occasionally suffered epizootics due to another orthopoxvirus—monkeypox virus (Magnus et al., 1959; see Chapter 29). Known outbreaks of monkeypox were reviewed by Arita & Henderson (1968), and early in 1969 the WHO Smallpox Eradication unit convened an Informal Group on Monkeypox and Related Viruses (see Chapter 29) to advise it on matters relating to the problem of an animal reservoir of variola virus. The following year one of the members of the Informal Group (Dr Svetlana Marennikova) recognized that the virus recovered from a suspected case of smallpox that had occurred in Zaire 2 years after the last outbreak of smallpox in the area (Ladnyj et al., 1972) was indeed monkeypox virus (Marennikova et al.,

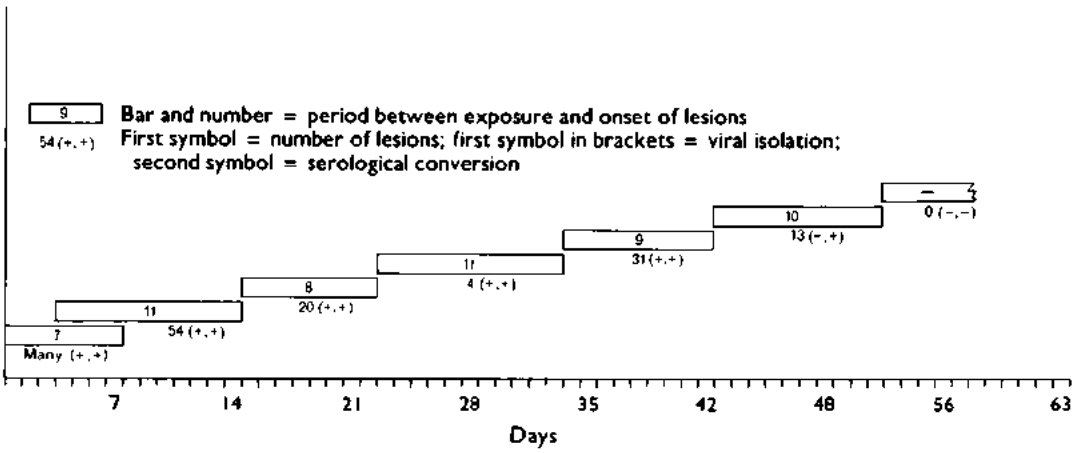

Fig. 30.1. Five successive contact infections of *Macaca irus philippinensis* before failure in transmission. The first monkey was infected by intranasal inoculation and after 7 days (indicated in bar) developed many lesions, from which variola virus was recovered (first "+" symbol) and subsequently showed serological conversion (second "+" symbol). The second monkey was placed in the same cage 3 days after the inoculation and developed 54 lesions 11 days after exposure; it was then placed in contact with the third monkey, and so on. The penultimate monkey in the series developed 13 lesions, but virus was not recovered from the crusts, although antibodies developed. The last monkey failed to develop lesions or convert serologically. (Based on Noble & Rich, 1969.)

1972b). Subsequently, human monkeypox has come to be recognized as a rare zoonosis apparently confined to villages in tropical rain forests in central and western Africa (see Chapter 29). The significance of human monkeypox in the present context lies in observations made in the course of ecological surveys in Zaire designed to elucidate the natural history of monkeypox virus. These resulted in a series of reports on what came to be called "wild whitepox" and ultimately "whitepox" viruses.

"Whitepox" Virus Isolations

Three sets of isolations of "whitepox" viruses have been made which are best dealt with separately and chronologically. The first set ("Netherlands isolates") comprises 2 strains, designated 64-7255 and 64-7275, apparently recovered from normal cynomolgus monkey kidney cell cultures at the National Institute of Public Health at Bilthoven (Gispen & Kapsenberg, 1966; Gispen & Brand-Saathof, 1972). The second

White Pock Mutants, "Whitepox" Viruses and White Clones (Variants) of Monkeypox Virus

The appearance of pocks produced on the chorioallantoic membrane by different species of *Orthopoxvirus* varies from bright red (cowpox virus), through a greyish ulcerated appearance with a haemorrhagic centre (monkeypox virus and some strains of vaccinia virus including rabbitpox virus) to a dense white pock with no sign of ulceration (variola virus, some strains of vaccinia virus and camelpox virus). All viruses that produce haemorrhagic pocks also yield a small proportion of non-haemorrhagic pocks; these are the "white pock mutants" of cowpox, rabbitpox, neurovaccinia or monkeypox virus, which have been used for genetic studies of orthopoxviruses.

In 1966 Gispen & Kapsenberg reported the recovery of orthopoxviruses from apparently normal cynomolgus monkey kidney cells used for viral diagnostic work in the National Institute of Public Health, Bilthoven. One of them was vaccinia virus; the other 3 were regarded as monkeypox virus. However, when studying these "monkeypox" virus isolates, Marennikova et al. (1971) showed that one of them resembled variola virus and was clearly distinguishable from monkeypox virus. Gispen & Brand-Saathof (1972) confirmed this result with 2 of the 3 "monkeypox" virus isolates and in the same paper observed that a white pock mutant that they recovered from monkeypox virus resembled the parental virus in most properties and was clearly distinguishable from variola virus. To discriminate between them, the variola-virus-like strains were called "wild white" poxvirus, or "whitepox" virus.

Between 1971 and 1975 Marennikova and her colleagues at the Moscow Research Institute for Viral Preparations reported that they had recovered white-pock-producing orthopoxviruses from the tissues of 4 species of animals shot in Zaire (chimpanzee, monkey, sun squirrel and multimammate rat). All isolates resembled Gispen's "wild white" poxvirus (and thus variola virus) in all the biological properties that they could test. For purposes of reference, the term "whitepox" virus was used to include all six of these viruses (Arita & Henderson, 1976).

In 1978–1979 Marennikova and her colleagues reported that they had obtained "whitepox" by inoculating monkeypox virus on the chorioallantoic membrane and in hamsters. They called these isolates "stable white clones" or "white variants" of monkeypox virus.

In this way two terms came to be used by virologists associated with the smallpox eradication programme:

(1) White pock mutants—of rabbitpox, cowpox and monkeypox viruses; and
(2) "Whitepox" viruses—from normal cynomolgus monkey kidney cells, from apparently normal wild animals shot in Zaire, or found as "stable white clones" or "white variants" of monkeypox virus.

set ("Zaire isolates") comprises 4 strains of virus reported by workers at the Moscow Research Institute for Viral Preparations to have been recovered from the tissues of 4 different species of wild animal captured in Zaire between 1971 and 1975 (Table 30.2). The third set ("white clones") comprises several isolates made from preparations of monkeypox virus maintained at the Moscow Research Institute for Viral Preparations (Marennikova & Shelukhina, 1978; Marennikova et al., 1979).

Netherlands isolates

During 1964 and 1965 4 orthopoxvirus isolations were made from cynomolgus monkey kidney cells that were being used for the

Laboratory Contamination with Viruses

Bacteriologists are accustomed to the idea that unwanted organisms may occasionally find their way into culture media and multiply there. Indeed, the discovery of penicillin resulted from one such episode (Fleming, 1929). Similar accidents may occur with viruses, especially if manipulations are of the kind that produce aerosols. Only a few cases of the contamination of cultures have been reported (e.g., Andrewes et al., 1944). Another kind of environmental contamination is the accidental infection of laboratory workers (see, for example, Pike, 1979; Wedum et al., 1972), which is an indicator of the possibility of infection of laboratory cultures.

H. Mahnel (personal communication, 1984), concerned about the occasional occurrence of vaccinia virus plaques on "uninfected" cell monolayers, carried out tests with vaccinia and monkeypox viruses under conditions simulating those in the laboratory. The infectivity of tissue culture fluid dried on coverslips and stored in Petri dishes in the shade in the laboratory (temperature 20–23 °C) dropped from $10^{5.8}$ plaque-forming units per ml to $10^{2.8}$ plaque-forming units per ml in 12 days, but the dried material did not completely lose infectivity until the 6th week. He believes that the principal source of laboratory contamination of cultured cells arises from droplets of infected fluid drying on bench tops and in the dust of the laboratory.

Although the risk of cross-infection can be reduced by good microbiological technique, there is an ever-present possibility of the contamination of tissue cultures or eggs. Almost every laboratory manipulation is associated with some risk of producing aerosol particles that could contain virus. Dimmick et al. (1973) have drawn up a table listing the "spray factors" of various laboratory operations and accidents. Assuming that a viral suspension contains 10^7 pock-forming units per ml, it is possible to calculate the number of infectious aerosol particles released as a result of normal laboratory operations or minor accidents.

Operation	*Spray factor*	*Virions per m^3 of working area*
Blender opened 5 minutes after stop	$10^{-5.3}$/min	50
Pipetting, minimal bubbling	$10^{-6.3}$/min	5
Intranasal inoculation of mice	$10^{-7.3}$/min	0.5
Drop spilled from a height of 100 cm	$10^{-6.3}$	5
Removal of plug from test tube	$10^{-8.5}$	0.03

The only certain way of avoiding cross-infection with poxviruses is to use only one isolate at a time, within a glovebox facility or a biocontainment hood, and thoroughly sterilize the working area before handling another strain of virus.

Without special markers and laborious experiments, it was very difficult to "prove" that laboratory contamination had occurred, as Dumbell & Kapsenberg (1982) were able to do, but every experienced laboratory scientist who has worked with poxviruses can recall instances for which he or she believed that contamination was the most likely cause of an unexpected result.

Table 30.2 Details of the circumstances of the recovery in Moscow of "whitepox" viruses from wild animals captured in Zaire

Viral isolates	Date of isolation	Antibody titrations[a]		Results of first CA membrane passage	Appearance of pocks with passaged virus	Repeat isolation	Comment	Reference
		HI	Neut.					
Chimp 9	February 1971	1280	40	Scanty lesions	Like variola virus	Positive 6 weeks later; from piece of kidney[b]	From kidney of 1 of 9 primates tested: chimpanzee (*Pan troglodytes*)	Marennikova et al. (1972b)
MK-7-73	February–March 1973	256	80	Pocks 0.5–1.0 mm	"	Negative	From kidney of 1 of 12 animals tested: "Sala" monkey (*Cercopithecus ascanius*)	Shelukhina et al. (1975); Marennikova et al. (1975)
RZ-10-74	October 1974	..	..	2 pocks, small, white and dense	"	Positive 4 weeks later; from ground suspension	From kidney of 1 of 12 multimammate rats (*Mastomys natalensis*) tested	Marennikova et al. (1976)
RZ-38-75	April–May 1975	..	80	1 pock on 1 of 3 membranes	"	Not tested	From kidney of 1 of 30 rodents tested: sun squirrel (*Heliosciurus rufobrachium*)	Marennikova et al. (1976)

[a] HI = haemagglutinin-inhibition; Neut. = neutralization of vaccinia virus on chorioallantoic (CA) membrane; figures indicate reciprocal of titre; .. = data not recorded.
[b] Special precautions to prevent contamination with variola virus were taken at time of relocation (personal communication from S.S. Marennikova).

isolation of viruses from human material in the diagnostic laboratory at the National Institute of Public Health, Bilthoven (Gispen & Kapsenberg, 1966). One strain (64-9411) was eventually diagnosed as monkeypox virus (see Chapter 29) and one strain (65-3993) was vaccinia virus, recovered together with herpes simplex virus from vesicle fluid (J. G. Kapsenberg, personal communication, 1981). The other 2 strains (64-7255 and 64-7275) were first regarded as monkeypox virus (Gispen & Kapsenberg, 1966); subsequently Marennikova et al. (1971) reported that strain 64-7275 differed from monkeypox virus in a number of biological characteristics but could not be differentiated from variola virus. This finding was confirmed by Gispen & Brand-Saathof (1972), who later showed that these 2 strains differed from monkeypox virus and resembled variola virus in tests for virus-specific antigens (Gispen & Brand-Saathof, 1974). Subsequently Esposito et al. (1978) and Dumbell & Archard (1980) demonstrated that the DNA electropherograms and restriction endonuclease maps of these 2 isolates, while differing slightly from those of some other strains of variola virus, identified them unequivocally as members of the variola virus species.

Although in a comment at the International Symposium on Smallpox Vaccine, Bilthoven, in 1972 Gispen (1973) stated, correctly, that "there was no known possible contact *of these animals* [from which the kidney cell cultures infected with whitepox virus had been derived; our italics] with pox viruses", it subsequently transpired that on 2 occasions in September 1964, material from smallpox patients from Vellore, India, had been handled in the diagnostic laboratory in which the cynomolgus kidney cells were being used. Skilful detective work by Dr Kapsenberg identified the passage transfer of cell cultures during which viral contamination could have occurred; there was a temporal coincidence with manipulation of the cynomolgus cells in question and cells infected with material from the smallpox cases. That laboratory contamination was the explanation was demonstrated with a high degree of confidence by the fact that the biological properties and restriction endonuclease electropherograms of strains 64-7255 and 64-7275 were identical with those of 1 of the 2 variola viruses isolated from the Vellore cases, which were slightly different from those of most

other strains of variola virus (Dumbell & Kapsenberg, 1982).

Zaire isolates

Five strains of poxvirus were recovered from the kidneys of wild animals captured in Zaire and processed in the Moscow Research Institute for Viral Preparations. Four were identified as "whitepox" viruses (Table 30.2), and the fifth (MK-10-73) as vaccinia virus.

Pocks were always scanty on the membranes on which they were first observed. All subsequent investigations, including detailed DNA mapping carried out independently in 2 laboratories (St Mary's Hospital, London, England, and the Centers for Disease Control, Atlanta, USA), have confirmed that the 4 strains of "whitepox" virus are indistinguishable from variola virus.

A priori it is difficult to believe that a virus which has such a narrow host range as variola virus should be recovered from the tissues of 2 species of healthy rodents that are common in and near tropical forest villages in Central Africa, the rat *Mastomys natalensis* (syn. *coucha*) and the sun squirrel *Heliosciurus rufobrachium*. This view is reinforced by the observation that variola virus and "whitepox" virus strain RZ-38-75, said to have been recovered from *Mastomys natalensis*, multiplied very poorly after intraperitoneal inoculation in that animal (T. Kitamura, personal communication, 1978).

Since the Moscow Research Institute for Viral Preparations functioned as one of the two WHO collaborating centres that carried out laboratory diagnosis of smallpox for the Intensified Smallpox Eradication Programme (see Chapter 10), specimens of variola virus were constantly being handled in the laboratories in which the "whitepox" virus isolates were made. The universal experience of laboratories which have handled orthopoxviruses, including the experience of the National Institute of Public Health in Bilthoven, just described, attests to the difficulty of avoiding occasional cases of laboratory contamination.

Two features caution against too ready an acceptance of this explanation for all the Moscow "whitepox" virus isolates: the positive orthopoxvirus antibody titres found in 3 of the 4 animals whose tissues apparently contained virus, and the reported reisolation of virus from part of the stored kidney of Chimp 9 (from a chimpanzee) and from a ground-up suspension of kidney tissue of RZ-38-75 (from a sun squirrel). However, investigations of the ecology of monkeypox in Zaire, reported in detail in Chapter 29, suggest that there may be several orthopoxviruses circulating among wild animals in the forests of Zaire; the antibody results signify prior infection with an orthopoxvirus, not necessarily variola virus or even monkeypox virus. Reisolation is the standard procedure for confirming the validity of suspicious isolates, but to be acceptable it must be carried out with material that had not been processed in the laboratory at the time the first isolation was made. This situation did not apply to the material from *Heliosciurus*, but it did apply to the kidney of the chimpanzee (S. S. Marennikova, personal communication, 1983), a species which is known to be susceptible to infection with variola virus (Kalter et al., 1979). However, Chimp 9 was one of the two "whitepox" viruses tested by Dumbell & Huq (1986), who showed that it resembled Asian rather than African strains of variola virus in its biological characteristics (see below).

The number of strains of variola virus whose DNAs have been mapped by restriction endonuclease cleavage is too small to allow any conclusions to be drawn about the

Plate 30.2. Farida Huq (b. 1942) undertook graduate studies with Dr K.R. Dumbell in London before assuming responsibility for the smallpox laboratory in Dhaka, Bangladesh. Besides carrying out diagnostic work she studied the viability of variola virus in scabs under tropical conditions.

Table 30.3. The distribution of 4 independent biological properties characteristic of Asian variola major virus according to the geographical origin of the strains tested[a]

Source of variola virus strains	Number of biological properties[b]				
	0	1	2	3	4
Indian subcontinent	0	0	0	5	13
Western Africa	4	2	1	0	0
Zaire	4	1	0	0	0
Whitepox viruses[c]	0	0	0	0	2

[a] Based on Dumbell & Huq (1986).
[b] The characters were: chick embryo virulence; ceiling temperature; haemadsorption on human embryo fibroblast monolayers; and haemagglutinin production in HEp 2 cells.
[c] Chimp 9 and MK-7-73 (see Table 30.2).

relationship of these "whitepox" isolates to other strains of variola virus from western or central Africa. However, comparison of 4 biological characteristics of 32 variola virus strains originating from the Indian subcontinent, western Africa or Zaire with those of the "whitepox" strains Chimp 9 and MK-7-73 (purportedly recovered from primates captured in Zaire) showed that these "whitepox" isolates had the same group of biological characteristics as the great majority of strains of Asian variola major and were quite unlike 12 strains of variola virus derived from western Africa or Zaire (Table 30.3). Dumbell & Huq (1986) concluded that these two "whitepox" viruses (Chimp 9 and MK-7-73) "did not enter into the chains of transmission which maintained human variola in West Africa".

In summary, and in view of the results set out in the next section, it seems likely that the "whitepox" virus isolates made in Moscow were due to laboratory contamination with Asian strains of variola virus.

"White clones" ("variants") of monkeypox virus

Seeking an explanation for the recovery of whitepox virus strains from the tissues of several species of wild animals from Zaire, Dr Marennikova postulated that they may have arisen as "white clones" of monkeypox virus, which was known to infect non-human primates in that country (see Chapter 29). Several investigators (Bedson, 1964; Gispen & Brand-Saathof, 1972) had previously isolated white pock mutants of monkeypox virus, but found them to resemble the parental virus rather than variola virus in properties such as species-specific antigenicity (Gispen & Brand-Saathof, 1974) and the pattern of their intracellular polypeptides (Harper et al., 1979). In this section attention will be focused on two reports of what Marennikova and her colleagues call "stable white clones" recovered from stocks of monkeypox virus that had been maintained for several years in the Moscow laboratory. All these "white clones", recovered either as pocks on the chorioallantoic membrane (Marennikova et al., 1979) or from organs of hamsters that had been inoculated some weeks earlier with the monkeypox virus material (Marennikova & Shelukhina, 1978), were identical; they were indistinguishable by biological tests from the Zaire and Bilthoven "whitepox" virus isolates, which have now been shown to be variola virus.

In view of the importance of this claim as to the origin of "whitepox" viruses, from the point of view of the feasibility of smallpox eradication, the WHO Smallpox Eradication unit organized a series of studies to determine whether these results could be independently confirmed. The studies in question were conducted in the WHO collaborating centres in London and Atlanta. Dumbell & Archard (1980) reported on 17 white pock mutants recovered on the chorioallantoic membrane from their own stocks of the Copenhagen strain of monkeypox virus and compared their biological characteristics and DNA maps with those of wild-type monkeypox virus, the Harvey strain of variola virus, the 2 Netherlands "whitepox" isolates, 2 Zaire "whitepox" viruses and 2 "white clones" recovered from monkeypox virus by passage through hamsters (Marennikova & Shelukhina, 1978). All the "whitepox" viruses and the 2 "white clones" had DNAs that were virtually identical with that of variola virus (Table 30.4). The monkeypox white pock mutants differed among themselves in both genome maps and biological properties (Table 30.5). Some, which had been recovered after serial passage of the monkeypox virus stock at high concentrations, showed complex genome changes, with deletions and transpositions; some showed minor differences from wild-type monkeypox virus, others were indistinguishable from it. In all cases the DNA maps were readily distinguishable from those of variola and "whitepox" viruses (Fig. 30.2).

Table 30.4. The derivations of various viral strains and the nature of their genomes as determined by restriction endonuclease analysis[a]

Strain		Recovered:		DNA analysis	
Characterization	Number	In	from	Pattern[b]	Laboratory
"Whitepox"	64-7255	Netherlands	Cynomolgus monkey kidney cells	var	Atlanta, London
"	64-7275	"	"	var	Atlanta, London
"	Chimp 9	Moscow	Chimpanzee, Zaire	var	Atlanta, London
"	MK-7-73	"	*Cercopithecus*, Zaire	var	London
"	RZ-10-74	"	*Mastomys*, Zaire	var	London
"	RZ-38-75	"	*Heliosciurus*, Zaire	var	London
"White clones"	Ham 8	Moscow	Passage of Moscow/Copenhagen monkeypox virus in hamsters	var	London
"	Ham 9	"			
"	CpMW	"	Moscow/Copenhagen monkeypox virus on CA membrane	var	Atlanta
"	CnMW	"	Moscow/Congo-8 monkeypox virus on CA membrane	var	Atlanta
White pock mutants of monkeypox virus	$CpCW_{N1}$	Atlanta	CDC-pock-purified Copenhagen monkeypox on CA membrane	mp	Atlanta
"	$CpCW_{N2}$	"	"	mp,del	Atlanta
"	$CpCn_{N1}$	"	CDC pock-purified Congo-8 monkeypox on CA membrane	mp	Atlanta
"	$CpCn_{N2}$	"	"	mp	Atlanta
White pock mutants of monkeypox virus	*h*16	London	London pock-purified Copenhagen monkeypox on CA membrane	mp	London
"	*h*2,15	"	"	mp,del	London
"	*h*3,4,5,6	"	"	mp,mod	London
"	*h*7,8,10	"	"		

[a] Based on Dumbell & Archard (1980) and Esposito et al. (1985).
[b] var = DNA pattern like that of variola virus; mp = DNA pattern like that of monkeypox virus; mp,del = DNA pattern like that of monkeypox virus, with terminal deletion; mp,mod = DNA pattern like that of monkeypox virus but with complex modifications.

Table 30.5. Phenotypic characteristics of white pock mutants of monkeypox virus

Virus		Pocks on chorioallantoic membrane		Lesions in rabbit skin after intradermal inoculation[a]	Growth at 35.5 °C in pig embryo kidney cells
		Appearance	Growth at 39 °C		
Monkeypox, wild type		Grey, haemorrhagic centre	+	Large, haemorrhagic	−
Variola (including "whitepox")		Opaque white	−	Slight transient erythema	+
Mutants:[a]	5[b]	Opaque white	+	..	−
	6	"	+	..	+
Mutants:[c]	3	"	*d*	Small nodule	−
	1	"	*d*	Small nodule	±

[a] Mutants described by Dumbell & Archard (1980).
[b] Numbers of mutants in each group. There were differences (not shown) within groups in the appearance of the white pocks, the size of the lesions produced in rabbit skin and the extent of growth in pig embryo kidney cells.
[c] Mutants described by Esposito et al. (1985).
[d] Not tested.

Studies at the Centers for Disease Control (CDC), in Atlanta, confirmed the results obtained in London. Four white pock mutants—2 derived in Atlanta from CDC stocks of a monkey strain of monkeypox virus (Copenhagen) and 2 from their stocks of a human strain (Congo)—resembled monkeypox virus in both their DNA maps (Table 30.4) and their biological characteristics (Table 30.5). On the other hand, Esposito et al. (1985) reported that isolations of white pock mutants made by a member of the staff of the Moscow laboratory working in the CDC, but not using the glovebox facility, had

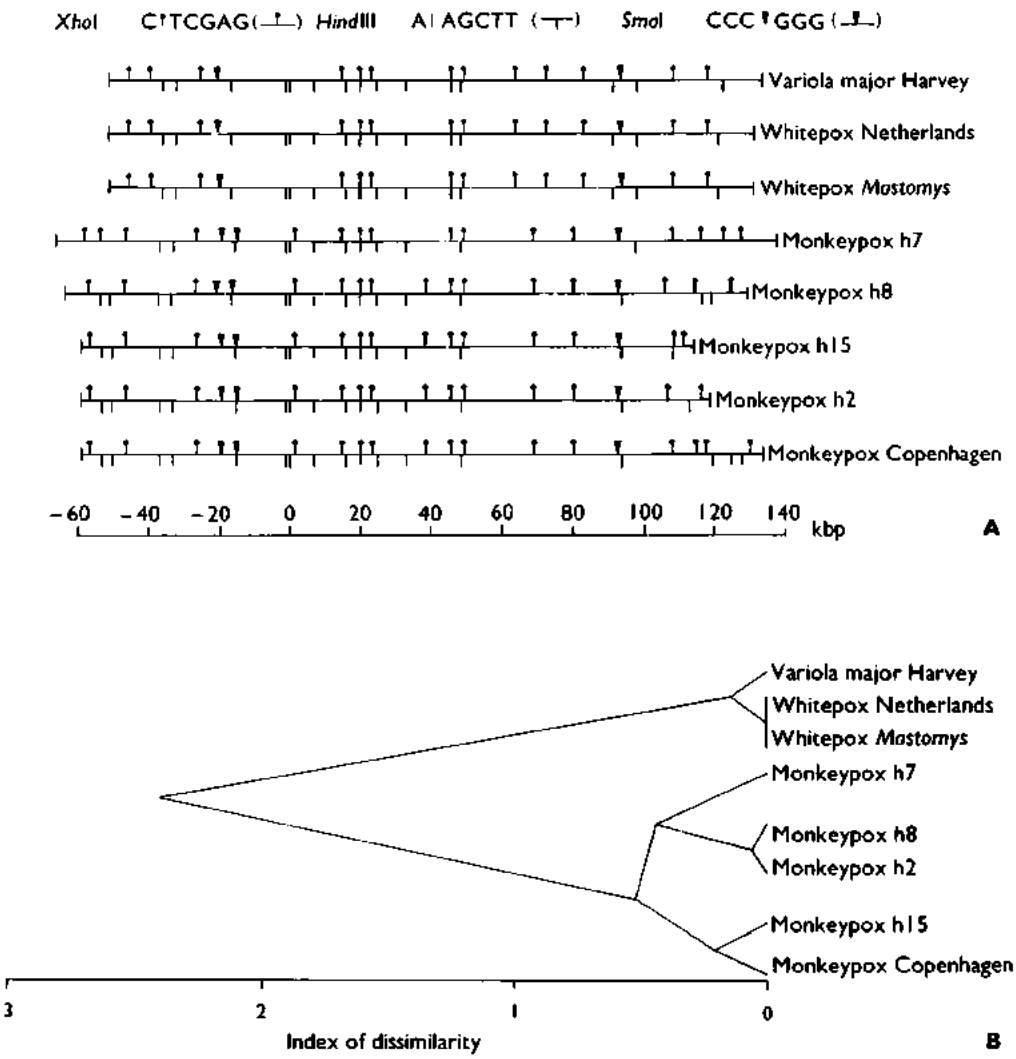

Fig. 30.2. **A**: Physical map locations of *HindIII*, *XhoI* and *SmoI* cleavage sites in DNA from variola, "whitepox" and monkeypox viruses: Harvey strain of variola major, Netherlands "whitepox" 64-7255, "whitepox" *Mastomys* (= Moscow RZ-10-74), Monkeypox Copenhagen, and 4 white pock mutants derived from Monkeypox Copenhagen (Monkeypox h2, h7, h8 and h15. (Based on Dumbell & Archard, 1980.) **B**: Dendrogram illustrating the similarities and differences between these DNAs. Presence, absence or impossibility (because DNA molecules were too small) of coincidence of the cleavage sites illustrated was determined after aligning all maps on a common *HindIII* cleavage site about 60 kilobase pairs from the left-hand end of the molecule; the results were then analysed as described by Gibbs & Fenner (1984), using the squared Euclidean metric (number of attributes = 60). The "index of dissimilarity" has no absolute value, but illustrates the close resemblances between the DNAs of variola virus and the 2 "whitepox" viruses, and between the DNAs of monkeypox virus and the 4 mutants derived from it.

biological properties and DNA maps identical with those of variola virus. On the basis of a detailed analysis of all the data, these authors concluded that "the spontaneous production of whitepox from monkeypox virus would be genetically impossible", and that "the whitepox viruses recovered from monkeypox virus stocks had originated exogenously".

This work was carried out in 1978 and 1979, and in an assessment of the situation in 1980, on the eve of the declaration of smallpox eradication by the Thirty-third World Health Assembly, Fenner et al. (SE/80.154) concluded that "the variety of mutants derivable from monkeypox in the laboratory does not present any greater threat to the success of smallpox eradication than

does the existence in nature of orthopoxvirus species other than variola".

Conclusion: There is No Animal Reservoir of Variola Virus

The evidence reviewed in the foregoing pages suggests that smallpox was indeed a specifically human disease. Variola virus is a distinctive species; DNA analysis of strains of widely differing virulence for man (variola major and variola minor viruses) shows that their DNAs are very similar, but quite different from those of any other species of orthopoxvirus or from those of any viral mutants that have been recovered under conditions that precluded the possibility of laboratory contamination. Variola virus has a narrow host range; besides man the only animals in which serially transmissible infection is known to have occurred are chimpanzees, orang-utans and one species of monkey. The "whitepox" viruses isolated from a variety of animals between 1964 and 1975 are strains of variola virus. The most acceptable explanation is that all of them were laboratory contaminants.

The laboratory evidence must be seen in both epidemiological and evolutionary perspectives. Apart from known contaminants (the Bilthoven viruses), the 4 "whitepox" viruses were recovered from areas of Zaire in which human monkeypox occurred and continues to occur more frequently than anywhere else in the world. The isolation rate in Moscow for the recovery of a virus from wild animals was high (4 out of 61 animals from the areas that were tested, compared with none of 930 animals from the area tested by the Centers for Disease Control, Atlanta, primarily in a search for monkeypox virus). Since human monkeypox is a zoonosis and intensive surveillance in selected areas of Zaire between January 1982 and December 1984 revealed 210 cases of human monkeypox, of which 144 were thought to have an animal source (see Chapter 29), there is clearly the kind of contact between humans and animals in these tropical rain forests that would make infection of humans with variola virus likely, if indeed it occurred in the animals there. However, all cases of "suspected smallpox" in western and central Africa since 1970 that were due to orthopoxvirus infection have been shown by epidemiological and laboratory investigation to have been caused by monkeypox virus.

MATERIAL STORED BY VARIOLATORS

Variolation was a matter of concern as a source of outbreaks of smallpox during the operations of the Intensified Smallpox Eradication Programme in Afghanistan, Pakistan and Ethiopia (see Chapters 14 and 21). In addition, it was known that an outbreak in northern Yunnan Province in China in 1958 was due to variolation, 126 cases having occurred a year after the last known case in that subregion. Late in 1984 it was learned from Dr Jiang Yutu, in a personal communication, that there had been other outbreaks of smallpox in North China (Nei Monggol Autonomous Region (Inner Mongolia) and 2 nearby counties in Shanxi Province) which were ascribed to the activities of variolators and the first of which occurred some 6 years after the last reported cases of smallpox in these regions (see Chapter 8, Table 8.13; and Chapter 27). The explanation for these outbreaks (Jiang Yutu, 1985; and personal communications, 1984, 1987) appears to be that variolators in Shanxi and adjacent parts of Inner Mongolia continued to keep variolation material, stored with honey in sealed jars, and maintained its potency by annual passage in susceptible family members and by the addition of fresh material to the jars. The 1962–1964 and 1965 outbreaks were initiated by such variolated persons but the chains of transmission have not been elucidated. The occurrence of these outbreaks long after smallpox had been eradicated from China led to measures that eliminated this source of the disease and no case of smallpox has been recorded in the country since 1965.

Apart from these episodes in China, which did not come to the attention of WHO until 1984, major concern with the danger of variolators' material causing outbreaks of smallpox after the interruption of transmission centred on Afghanistan. Tests for viable virus in material collected from variolators there gave positive results in one sample 9 months after the material had been collected from a patient; all the others were negative long before this (see Chapter 14, Table 14.15). All the variolators who were questioned about their mode of operation said that, if it was available, they preferred to use fresh material (from a recent case), and as smallpox became less common they usually added fresh

scabs or pustule fluid to their stored material whenever possible. One sample tested contained herpesvirus particles, doubtless derived from a misguided attempt to keep viable stocks for variolation.

Within scabs, out of sunlight and in cool surroundings, viable variola virus can survive for several years. However, variolators' material was never held under such "ideal" conditions, and tests showed that it rarely contained viable virus for as long as one year. The major factor that now further reduces the risk presented by variolation material as a source for the recurrence of smallpox is the passage of time. The last cases of smallpox in countries in which variolation was widely practised during the 20th century occurred in 1965 (China), 1973 (Afghanistan), 1974 (Pakistan) and 1976 (Ethiopia). In Ethiopia, in which smallpox was the most recently endemic, variolation was usually carried out with fresh pustular material when an epidemic threatened, and material was rarely stored (see Chapter 21). The lapse of 10–20 years since the last cases of smallpox in the other countries has reduced the incentive to practice variolation, and even under the best storage conditions (short of refrigeration) the viability of variola virus gradually falls off. The absence of any recurrence of smallpox due to variolation for 10 years or more gives reason to believe that this practice will never again initiate an outbreak of smallpox.

LABORATORY STOCKS OF VARIOLA VIRUS

While the existence of an animal reservoir was without doubt the most serious risk to the achievement of the permanent eradication of smallpox, the existence of stocks of variola virus in laboratories constituted and, while such stocks of variola virus are retained, will continue to constitute a real though remote risk that further cases of human smallpox could occur.

Changes in Attitude towards Work with Variola Virus

The handling of variola virus has been subject to progressively stricter control over the years. In Jenner's day variolation was extensively practised, with no control or supervision of the way in which the virus was handled or administered and usually little or no check on the movements of the inoculated subject. Jenner, and vaccinators after him, did not hesitate to test the efficacy of vaccination by challenge inoculation with variola virus. Variolation, which involved the uncontrolled distribution of variola virus, was not made illegal until 1840 in Great Britain and 1870 in British India, and, as has been noted above, it was widely practised in Afghanistan up to the early 1970s and in Ethiopia until as late as 1976.

Pathologists who were interested in smallpox and vaccinia experimented with variola virus as a matter of course and with few precautions, secure in the protection afforded by a previous attack of smallpox or by repeated vaccination. The attitude of virologists towards handling the virus in the 1950s is revealed in the report on experiments on viability by Wolff & Croon (1968), who stored scabs from a patient in an envelope in a cupboard in their laboratory in 1954, and tested one scab annually for the presence of variola virus. At that time reliance was placed on vaccination and revaccination of all laboratory workers, good laboratory technique, and careful disposal and sterilization of infected material and glassware. Biohazard hoods had not then been invented and work with variola virus was carried out on open benches, although special cubicles were sometimes used when the virus was handled on a large scale. In countries in which smallpox was still endemic—for example, in India, Africa and South America—material for smallpox diagnosis was regarded, with reason, as being less hazardous to handle in the laboratory than, for example, material containing the tubercle bacillus.

Safety Regulations in Laboratories Holding and Handling Variola Virus

Recommendations made in 1969 and 1974

The first comment by WHO on precautions to be taken when handling variola virus in the laboratory appeared in the publication *Guide to the Laboratory Diagnosis of Smallpox for Smallpox Eradication Programmes* (World Health Organization, 1969a), which was prepared by 2 virologists with extensive experience in handling variola virus (Dr A. W. Downie and Dr J. Noble) and 2 epidemiologists (Dr I. Arita and Dr A. S. Benenson). The guide suggested that methods

that ensured high standards of microbiological safety should be employed and that everyone who might have occasion to enter the laboratories should be vaccinated annually. However, recommendations on physical containment were relatively simple (Fig. 30.3A) —a separate room entered via a vestibule, but no provision for sterilization of the ambient air, for biosafety hoods or for 2-way autoclaves.

Following the accidental infection of a laboratory worker in London in 1973 (see Chapter 23), virologists in the United Kingdom interested in smallpox drew up a code of safety practice (Cox, 1974). This code formalized arrangements for vaccination and revaccination and for the first time suggested the use of safety cabinets and emphasized the risk of aerosol production during laboratory manipulations. It recommended that animal inoculation should be performed only in "institutes with specially designed facilities".

During the middle and late 1970s laboratory safety in general became a much more prominent issue. There were several reasons for this, including deaths from Lassa and Marburg fevers contracted in the laboratory, the invention and development of sophisticated methods for the physical containment of infectious agents, and the widespread concern for laboratory safety engendered by the introduction of recombinant DNA technology.

Safety measures recommended by WHO in 1977

Because of this change in attitude towards laboratory safety, and the imminent achievement of the global eradication of smallpox, the WHO Smallpox Eradication unit in August 1977 organized a meeting of experts to discuss safety measures in laboratories retaining variola virus. The expert group included senior staff from the WHO collaborating centres for smallpox research in London, Tokyo, Moscow and Atlanta, and Dr J. H. Richardson of the Office of Biosafety at the Centers for Disease Control, Atlanta. Recommendations for physical containment and the packaging and shipping of specimens were drawn up (SME/77.2). Although smallpox laboratories in the WHO collaborating centres had to a greater or lesser degree already installed the physical facilities outlined in this report, it was the first official statement by WHO prescribing the kinds of physical containment necessary for holding and handling dangerous pathogens, with strict control of entry, facilities for air and biowaste sterilization, gloveboxes (see Plate 30.3), 2-way autoclaves and biological safety cabinets (see Fig. 30.3 B), as well as the usual stipulations about vaccination and regular revaccination.

The laboratory-associated outbreak in Birmingham, England, in August-September 1978 (see Chapter 23) caused serious concern among the general public and the health authorities of many countries. Reacting to this concern, the WHO Smallpox Eradication unit arranged a meeting in Geneva in April 1979 to study the safety measures adopted in laboratories then retaining stocks of variola virus and to discuss the destruction or transfer of the virus if the laboratory concerned was not using it for research. Government officials from the 7 countries and scientists from the 8 laboratories that then retained variola virus attended the meeting and reviewed the situation (WHO/SE/79.137), with special reference to the role of national authorities in maintaining safety standards. They agreed on modifications to the WHO recommendations for physical containment in accordance with further experience with such facilities; these were issued as WHO document SME/77.2 Rev. 1 and later reproduced in Annex 9 to the final report of the Global Commission (World Health Organization, 1980). Eventually, in March 1983, the WHO Committee on Orthopoxvirus Infections, noting that the Organization, through its Special Programme on Safety Measures in Microbiology, had published a book entitled *Laboratory Biosafety Manual* (World Health Organization, 1983) which provided a standard reference for a maximum containment laboratory, recommended that WHO document SME/77.2 Rev. 1 should be withdrawn.

Over the several years after the 1977 meeting steps were taken to ensure that the facilities in the WHO collaborating centres in Atlanta and Moscow were upgraded, and new laboratories were built in each centre. It is not widely appreciated how difficult it is to build a highly secure biocontainment laboratory and maintain it properly, particularly in relation to airflow. For various reasons it took more than 3 years to construct and test the new facilities in both centres, and all research work with variola virus ceased during this period, although studies with variola virus DNA, which is not infectious, continued in

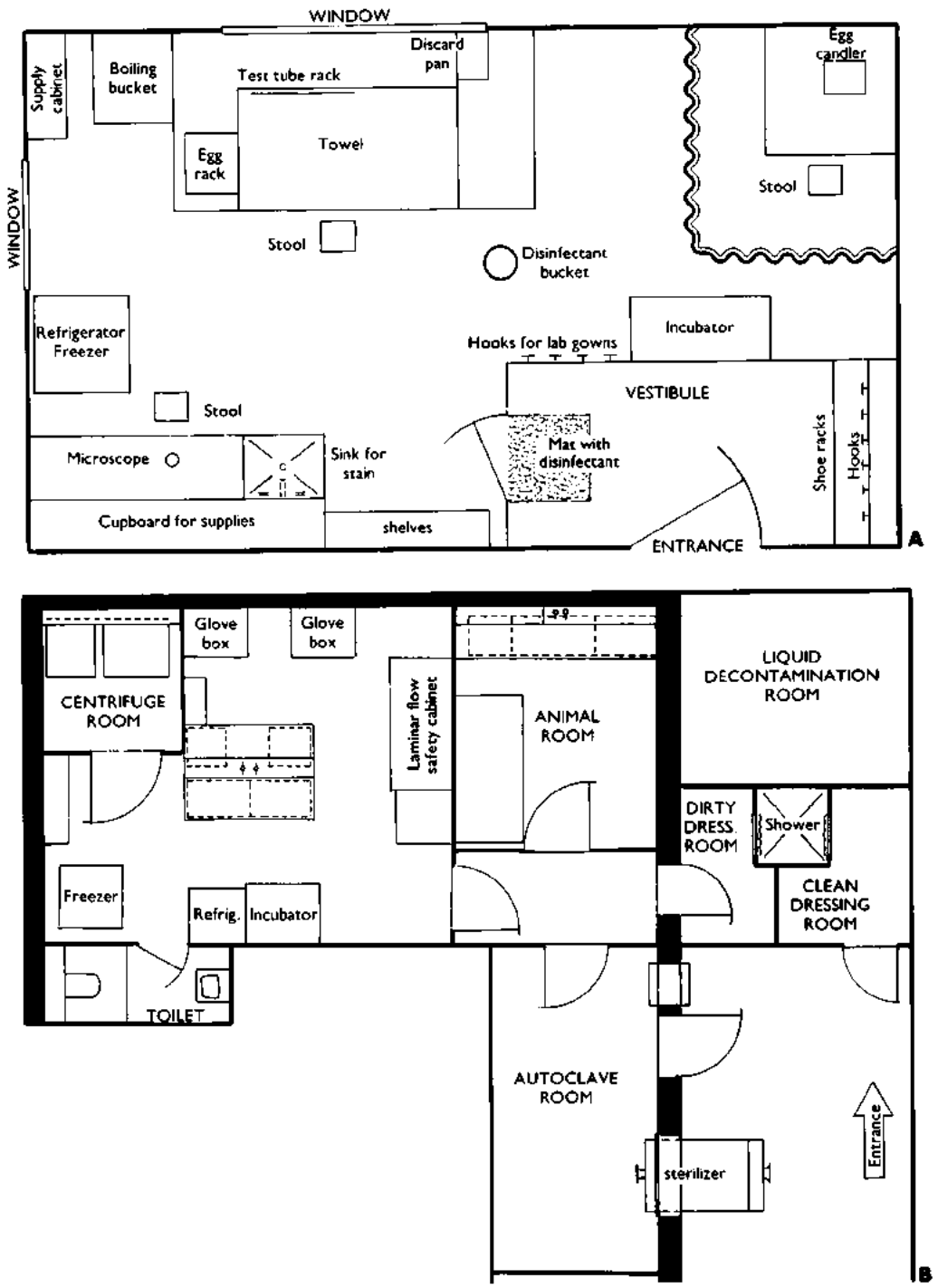

Fig. 30.3. **A**: Suggested layout for a smallpox diagnostic laboratory as conceived in 1969. (From World Health Organization, 1969a.) **B**: Plans of part of the smallpox laboratory at the Centers for Disease Control, Atlanta, GA, USA, drawn in 1979. Note the much more stringent physical containment, with access and exit of personnel through a shower and access of materials through a decontamination box and exit via a two-way autoclave. Effluent air is passed through a HEPA (high-efficiency particulate air) filter and liquid and solid wastes are sterilized by heat treatment. Within the laboratory, virus is handled within a glovebox or under a laminar flow hood and special precautions are taken with centrifugation and other laboratory manipulations.

Plate 30.3. Glovebox facility (Class III biological safety cabinet) in use at the WHO collaborating centre in the Centers for Disease Control, Atlanta, GA, USA. To eliminate the risk of laboratory contamination, only a single specimen was handled at a time and the cabinet was sterilized with peracetic acid before another specimen was introduced.

Atlanta. Between August 1981 and March 1983 urgent diagnostic work on specimens from cases of suspected smallpox or monkeypox was carried out in the Special Viral Pathogens Laboratory at the Centers for Disease Control in Atlanta. Work with variola virus in other laboratories that held the virus in 1979 (see Table 30.6) ceased at various times between 1979 and 1982, when their stocks were transferred to a variola virus storage facility in the Centers for Disease Control.

Two of the 19 recommendations of the Global Commission (World Health Organization, 1980), all of which were accepted by the Thirty-third World Health Assembly in May 1980, dealt with the inspection of WHO collaborating centres approved to hold and handle variola virus. It was recommended that each laboratory that still held variola virus (whether or not a WHO collaborating centre) should report annually to WHO on its safety measures and should be inspected periodically by WHO. The implementation of these recommendations has been described in Chapter 28.

Justification for the Retention and Use of Variola Virus

The potential danger of experimentation with variola virus in a laboratory not equipped with full microbiological security facilities was dramatically demonstrated by the Birmingham outbreak, discussed in Chapter 23, some 10 months after the last known case of naturally transmitted smallpox had been reported in Somalia. In response to the concern expressed by many WHO Member States, a consultation of public health and virological experts who were not themselves involved in laboratory work with variola virus was convened in Geneva in February 1979. Its report (WHO/SE/79.135) was subsequently used by the Global Commission for the Certification of Smallpox Eradication in formulating its final report (World Health Organization, 1980). In essence, the consultation recommended that research with variola virus was justified, at least for the next 3 years, because of the problem then posed by reports of the isolation of "whitepox" viruses and the work on DNA mapping that provided a

The Maximum Containment Laboratory

The 1977 report and the *Laboratory Biosafety Manual* recommended the use of a maximum containment laboratory for the handling of dangerous pathogens. In essence, this is a room or a few rooms (or, for veterinary laboratories handling exotic viruses, a complete laboratory building) in which special measures are taken for the physical containment of dangerous pathogens, to minimize the risk of their escape outside the laboratory. The principal features of a maximum containment laboratory are:

(1) *Controlled access.* The entry and exit of personnel and supplies are through airlock systems. On entering, personnel put on a complete change of clothing, and they shower on exit before changing back into their street clothes.

(2) *Controlled air system.* Negative pressure is maintained by an individual supply and exhaust air mechanical ventilation system with HEPA (high-efficiency particulate air) filters in the exhaust (and in the intake when necessary).

(3) *Decontamination of effluents.* All effluents from the maximum containment laboratory are rendered safe, including the shower water.

(4) *Sterilization of waste and materials.* A double-door pass-through autoclave is provided.

Properly installed, operated and maintained, these arrangements should prevent the escape of dangerous pathogens from such a laboratory. To protect personnel from infection and to minimize the risk of contamination of apparatus and cultures, an additional facility can be operated within the maximum containment laboratory. This is called the *primary containment facility*, of which there are 3 forms:

(1) a fixed "Class III" biosafety cabinet (Plate 30.3), in which material is handled via glove ports and all effluent air is passed through a HEPA filter,

(2) a flexible-film plastic equivalent of a Class III biosafety cabinet, or

(3) a positive-pressure ventilated suit, operated only in a special laboratory which provides a decontamination shower for personnel leaving the risk area.

The WHO collaborating centre in Atlanta handled all specimens of known or suspected variola virus within a Class III biosafety cabinet. One specimen was handled at a time and the cabinet sterilized with peracetic acid before another specimen was introduced. This practice enabled that laboratory to avoid completely any cases of laboratory contamination of cultures by its personnel, throughout its operations in smallpox diagnosis and research.

method of at least partially solving this problem. In January 1979, the WHO Executive Board had asked the Secretariat to recount what measures were being taken in response to the Birmingham outbreak. The Smallpox Eradication unit was able to inform the Board of the proposed consultation and the anticipated meeting on laboratory safety measures, mentioned in the previous section, which were designed to deal with the essence of the problem—namely, whether further research with variola virus was necessary and, if so, whether the laboratories in which such work was undertaken were microbiologically secure.

Reduction in the Number of Laboratories Retaining Variola Virus

The possibility of escape of variola virus from either of the two high-security laboratories that now retain it is extremely remote. But in 1976, as global smallpox eradication appeared imminent, stocks of the virus were held by many more than these two laboratories; in fact, no one knew how many more. It was reasonable to argue that the smaller the number of laboratories holding variola virus, the lower would be the risk of the virus escaping. The Twenty-ninth World Health Assembly, in May 1976, requested "all

Philosophical Considerations regarding the Destruction of Variola Virus

From time to time commentators in scientific journals have questioned the moral rectitude of destroying all known stocks of variola virus, on the grounds that man should not knowingly cause the extinction of any living thing. With the cloning of variola virus DNA this raises some interesting philosophical problems. Are variola virions, in an ampoule, "living things"? In fact they are inert until their genetic potential can be expressed, and the only "natural" form of living variola virus would be that found in a human being, since man was the only known host of the virus. Presumably, the periodic occurrence of cases of smallpox is not what conservationists have in mind when they argue that variola virus stocks should never be totally destroyed.

The other problem is whether the cloned fragments of variola virus can be regarded philosophically as still constituting the essence of life of that virus. Certainly, molecular biologists are, or soon will be, able to produce all the known viral products from such cloned fragments. They could even, with considerable (albeit misguided) effort, reconstitute the intact variola virus DNA molecule and thus by laboratory manipulations, the virus itself.

When viewed against the regrettable but wholesale extinction of species that results from human interventions in natural ecosystems, concern about the preservation of variola virus seems to us to be misplaced. The only criterion by which to judge the necessity for the preservation of the virus, we believe, is whether it is necessary for scientific work.

governments and laboratories to cooperate fully in preparing an international registry of laboratories retaining stocks of variola virus" but, at the same time, urged all laboratories which did not require such stocks of variola virus to destroy them (resolution WHA29.54). This resolution followed inquiries that the WHO Smallpox Eradication unit had addressed in 1975 both to governmental authorities and to the directors of 823 laboratories included in the WHO World List of Virus Laboratories. The unit had also scanned the *Index medicus* in search of references to papers on variola virus published from laboratories during the previous few decades and had written to the directors of these laboratories to find out whether they held stocks of the virus. This information having been obtained, laboratories other than the WHO collaborating centres in Atlanta and Moscow and the WHO laboratories for poxvirus research were asked to destroy their stocks or transfer them to one of the two WHO collaborating centres. Governments were asked to inform WHO of the response to this request. Prior to this, the Director of the National Smallpox Eradication Programme in India had carried out a similar survey in that country and reported that by the end of 1976 all stocks of variola virus in laboratories in India had been destroyed (Basu et al., 1979). The situation in the 6 WHO regions in 1975 and in July 1977 is shown in Table 30.6.

Some noteworthy inferences can be drawn from this table. First, the response from both national authorities and laboratory directors was remarkably comprehensive. Apart from China, the countries that failed to respond were small in size and population and were known not to have a laboratory that had ever handled variola virus. Secondly, there were no fewer than 75 laboratories, several in each WHO region, that were then holding variola virus. Indeed, the real figure was somewhat higher, for it is known that virologists in several laboratories discovered that they did still possess variola virus, after having, in good faith, declared to the contrary; in such instances, the stocks were privately destroyed or taken to the nearest WHO collaborating centre for destruction. This widespread possession of stocks of variola virus is not surprising. Smallpox was endemic in several populous countries and importations into Europe, especially, had occurred in the recent past. In order to have "controls" for the

Table 30.6. Laboratories holding variola virus stocks in 1975 and the reduction in this number by July 1977, in response to requests from WHO

WHO region	Number of countries		Number of laboratories		By July 1977	
	Information sought	Responded	Responded to WHO	Holding variola virus in 1975	Destroyed or transferred variola virus	Retained variola virus
Africa	46	43	15	5	4	1
Americas	34	34	506	18	13	5
South-East Asia	11	11	57	13	13	0
Europe	36	36	185	29	19	10
Eastern Mediterranean	23	23	25	3	3	0
Western Pacific	31	29	35	6(7)[a]	5	1(2)[a]
Total	181	176	823	74(75)	57	17(18)

[a] Although China did not respond to the WHO letter of request, stocks of variola virus were then held at the Institute for the Control of Drugs and Biological Products, Beijing.

laboratory diagnosis of agents that they rarely handle, such as variola virus, virologists usually keep strains of these agents in their deep-freeze cabinets, for comparison with a suspicious isolate. Provided that their staff were regularly vaccinated and used good microbiological techniques, laboratory directors rightly regarded variola virus as less dangerous to handle than other agents sometimes encountered in diagnostic laboratories, such as various rickettsias. Further, even though smallpox might no longer be endemic in their country, it did not occur to them to destroy their laboratory stocks of variola virus. However, in response to the request from WHO, and bearing in mind the imminent world-wide eradication of smallpox, the directors of 57 of the 74 laboratories agreed to destroy or transfer their stocks of the virus.

Further reduction in the number of laboratories retaining variola virus, 1977–1983

With strong support from the Consultation on the Worldwide Certification of Smallpox Eradication, convened in Geneva in October 1977, and subsequently from the Global Commission, WHO continued to exert pressure to try to reduce further the number of laboratories holding variola virus stocks. In its final report in December 1979 (World Health Organization, 1980) the Global Commission recommended that: "No more than four WHO collaborating centres should be approved as suitable to hold and handle stocks of variola virus. A collaborating centre would be approved only if it had adequate containment facilities." Biocontainment standards had been laid down for such laboratories (SME/77.2 Rev. 1) and it was stipulated that each laboratory that held variola virus (whether it was a WHO collaborating centre or not) should be periodically inspected by WHO.

The Birmingham outbreak had a dramatic effect on the attitudes of the directors of several European laboratories, because of Professor Bedson's suicide and the extensive press coverage of the event (see Chapter 23). By the end of 1979, 5 of the remaining 8 European laboratories holding variola virus had disposed of their stocks (Table 30.7). Every year, at the World Health Assembly, Member States continued to express concern about variola virus stocks in laboratories. Gradually, the remaining laboratories holding such stocks responded to the requests from WHO to destroy or transfer their holdings, since with the eradication of smallpox the rationale for retaining stocks of the virus in any laboratory except the WHO collaborating centres in Atlanta and Moscow had disappeared. Scientific developments, notably the cloning of restriction fragments representing the total genome of variola virus (see Chapter 2), removed the last objections,

Table 30.7. Laboratories holding variola virus stocks at the end of calendar years 1977–1983

Continent	1977	1978	1979	1980	1981	1982	1983
Africa	1	1	1	1	1	1	0
America	5	3	2	1	1	1	1[a]
Asia	2	1	1	1	0	0	0
Europe	10	8	3	3	2	1	1[b]

[a] WHO collaborating centre at the Centers for Disease Control, Atlanta, USA.

[b] WHO collaborating centre at the Moscow Research Institute for Viral Preparations, Moscow, USSR.

voiced by the Ministry of Health of South Africa (see Chapter 28, Plate 28.4), and by the end of 1983 only 2 laboratories in the world, both with newly completed biocontainment facilities, still held stocks of variola virus: the WHO collaborating centres at the Centers for Disease Control, Atlanta, and the Moscow Research Institute for Viral Preparations. At a meeting in March 1986, the Committee on Orthopoxvirus Infections recommended that all stocks of variola virus should be destroyed in October 1987, subject to approval by an *ad hoc* committee to be convened by WHO.

There remains the possibility that ampoules containing variola virus may still be stored in deep-freeze cabinets in laboratories, unknown to anyone in the laboratory or indeed in the country concerned. In most laboratories deep-freeze cabinets are rarely thoroughly cleaned out, though sections of them may be. As staff replacements occur and smallpox recedes into the past, all memories of working with variola virus will be lost. Two such incidents have come to the notice of the WHO Smallpox Eradication unit—the discovery of variola virus stocks in a laboratory in California in 1979 (Emmons, 1979), and in a laboratory in the United Republic of Tanzania during the visit of a WHO international commission in 1979 (J. G. Breman, personal communication, 1979). Another possible but unconfirmed example was described in London in December 1985. The dangers posed by such forgotten material are very small provided the laboratory carries out the recommended safety measures—namely, the destruction by autoclaving of any unlabelled ampoules or any ampoules labelled "variola virus" or "smallpox virus". This risk is hypothetical and in any case beyond the control of WHO or any other organization.

DELIBERATE RELEASE

The United Nations (1970) and a WHO group of consultants (World Health Organization, 1970) both included the smallpox virus among some 20 infectious agents that could be used in biological warfare. However, it ranked low in suitability compared with several other viruses, rickettsias and bacteria. As the WHO consultants commented:

"Because of the effectiveness of the vaccine and the relative ease with which it can be produced and administered, it is unlikely that smallpox virus would be used as an agent for a large-scale biological attack against countries systematically practising periodic vaccination.

"The variola virus, however, can easily be employed for acts of sabotage. Such acts, at selected points within a country, could have serious socio-economic effects unless efficiently dealt with by the public service."

That was written in 1969. At present no country is "systematically practising periodic vaccination" and as time passes the immunity of those who have been vaccinated will wane and populations will become completely susceptible.

In 1972 many countries of the world signed a convention outlawing the use of biological weapons in warfare (United Nations, 1984). Unfortunately, as international conventions are subject to infringement, this does not completely exclude the possibility that variola virus might be deliberately released as a means of warfare. However, the risk of any such act leading to the re-establishment of endemic smallpox should not be exaggerated. As has already been mentioned, smallpox spread comparatively slowly, by face-to-face contact. Unless the public health services had completely broken down, the existence of reserve stocks of vaccine (see Chapter 28) and the capacity for the production of vaccine to be rapidly reactivated would ensure the containment of any outbreak that followed a deliberate release of variola virus. With the cessation of vaccination and vaccine production, it will become increasingly difficult for any person or group contemplating the release of variola virus to assure themselves and their colleagues of protection against smallpox. A country's resumption of vaccination against smallpox would now be interpreted as a sign that it might be considering the use of variola virus for aggressive purposes.

Deliberate release, or the threat of it, by an individual or a group, as an act of sabotage or terrorism, is remote because access to the virus is so restricted. A document made public in December 1984 (Young & Lenarcic, 1984) describes tests made in 1964 and 1965 with aerosols containing *Bacillus subtilis* as a marker. The aerosols were experimentally but secretly produced in a crowded airport in Washington, DC, USA, to test the possibility that variola virus might be released in this way and thus cause "inexplicable" outbreaks of smallpox a few weeks later in the diverse

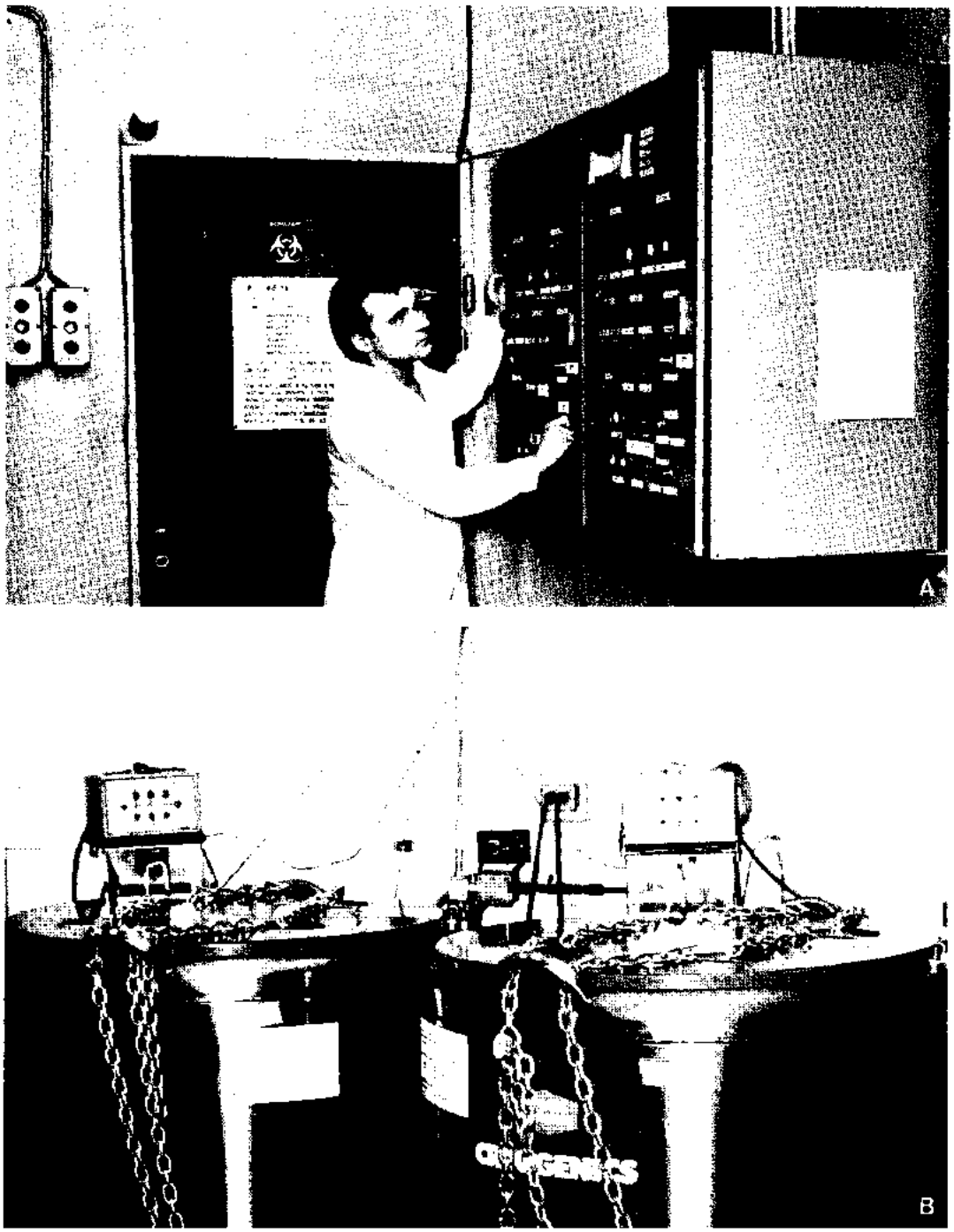

Plate 30.4. Only 2 laboratories in the world retain variola virus. **A**: Entrance to the maximum containment laboratory at the Moscow Research Institute for Viral Preparations, USSR. The control panel for biowaste disinfection and disposal is on the right and on the door is a list of persons authorized to enter. The door is kept locked and the key retained by the director. **B**: Variola virus is stored in two nitrogen vapour phase freezers in a maximum containment laboratory at the Centers for Disease Control, Atlanta, GA, USA.

places to which infected passengers travelled. The existence of such a possibility emphasizes the need for "military" as well as microbiological security in laboratories holding variola virus stocks. It is melancholy but perhaps realistic to suggest that the possibilities of biological warfare or terrorism now constitute the chief reason for holding reserves of vaccine and for maintaining epidemiological and laboratory expertise for the diagnosis and control of smallpox.

REACTIVATION AND EXCRETION OF VIRUS IN HUMANS

Viruses of many viral families persist for long periods in their hosts and viruses in some families are persistently (Arenaviridae) or intermittently (Herpesviridae) released into the environment. In addition, there is now a vast experience of the reactivation of latent herpesvirus infections (especially cytomegalovirus) in immunosuppressed persons, both those suffering from lymphoreticular diseases and those in whom chemical suppression of cell-mediated immunity is employed to prevent transplant rejection. In addition, steroid therapy has immunosuppressive effects and is associated with the reactivation of latent infections. Such therapies have now been practised for many years, in many countries, but no evidence has ever come to light of the reactivation of variola or vaccinia virus in immunosuppressed persons or those on steroid therapy. This supports the view elaborated in Chapter 3 that the poxviruses in general and variola and vaccinia viruses in particular do not produce persistent infections. This hypothetical possibility can be dismissed.

VIRAL PERSISTENCE IN THE ENVIRONMENT

Although it does not cause persistent infection in man, variola virus in scabs is, for a virus, very resistant to inactivation, especially at moderate temperatures and out of sunlight. Clothing and bedding from smallpox cases, which were often heavily contaminated with virus from salivary excretions and skin lesions, were an occasional source of outbreaks of smallpox among laundry workers (England and Wales, Ministry of Health, 1928b), and virus on imported raw cotton was suspected (without good reason, according to Dixon, 1962) of causing some outbreaks in England. However, the periods for which the virus survived to cause such infections were measured in days or weeks—not years.

Interred corpses have also been suggested as a possible source of infectious virus (e.g., Razzell, 1976), but the only evidence is anecdotal and comes from situations in which the possibility of infection by direct contact with cases of smallpox could not be excluded. The chance of viable variola virus surviving in corpses or coffins for the length of time that has elapsed since there were numerous smallpox deaths in temperate climates seems to us to be extremely remote, and the topic does not lend itself to scientific investigation.

A more bizarre possibility has been raised by Ewart (1983). Noting that bacteria can be preserved in permafrost for years (Boyd & Boyd, 1964), he suggested that active variola virus might still be preserved in interred bodies at York Factory on the shores of Hudson Bay in northern Canada. Six Indians were reported to have died of smallpox there in 1782, and it was the practice to inter the bodies of the dead in wooden coffins, which were placed in graves hacked out of the rock-hard earth of the permafrost. Most of this graveyard has now been eroded by the nearby Hayes river, but Ewart's contention is that variola virus could be preserved for long periods in some such way, somewhere in the Arctic. Whether viable variola virus could be released from a thawed corpse in such a way as to infect a susceptible person is a matter of conjecture. There is no scientific evidence on which to base a firm reply to speculations of this kind; one can merely say that the circumstances that would give rise to infection from such a source are exceedingly remote and impossible to study.

In whatever form the virus may persist in the environment, it is gradually inactivated, probably even at subzero temperatures (see Chapter 2). As the intervals since the last cases of smallpox in various parts of the world have extended from months to years and now to decades, this danger has lessened until it must now (1987) be considered to be very small indeed.

"TRANSFORMATION" AS A SOURCE OF VARIOLA VIRUS

The term "transformation" belongs to an era predating the development of microbial

BY COURTESY OF P. HERRLICH, 1967

Plate 30.5. Albert Herrlich (1902 – 1970), a leading German virologist and public health expert who was Director of the Institute for Comparative Tropical Medicine at the University of Munich. He was principal author of major books on the poxviruses and on vaccination and carried out a definitive study which showed that variola virus could not be "transformed" into vaccinia virus by passage in laboratory animals or cattle.

genetics. It now has a specific meaning: the alteration of the genome of a bacterium or eukaryotic cell by the incorporation of DNA from another source. As it used to be applied to the orthopoxviruses, the term was most frequently used to describe what was regarded as the conversion of variola virus into vaccinia virus, usually by passage through cows. It is impossible to achieve any such change when experiments are carried out under conditions that rigidly exclude the possibility of contamination (Herrlich et al., 1963).

The "white clones" of monkeypox virus, described above, were viewed by Marennikova and her colleagues as examples of the "transformation" of monkeypox into variola virus, but the evidence presented earlier argues strongly that these isolates arose because of the contamination of monkeypox virus stocks with variola virus. Likewise, there is no likelihood that either vaccinia or cowpox virus, of which suitable strains yield a great variety of white pock mutants, could give rise to variola virus by one or a few mutational steps. The clear-cut distinctions in the DNA maps of different species of *Orthopoxvirus* (see Chapter 2) preclude such a possibility.

GENERAL CONCLUSIONS

At this time, 10 years after the last known case of endemic smallpox, there is only one credible source from which another case of smallpox might arise—namely, the infection of a susceptible person with variola virus held in storage, either in a known location (stocks held in the WHO collaborating centres in Atlanta or Moscow) or in an unknown place. The latter could be either a stock maintained for possible use in microbiological warfare or a forgotten and possibly unlabelled specimen lying in a deep-freeze cabinet in a laboratory in which smallpox diagnosis or research was once performed. The likelihood of variola virus still surviving on scabs or associated with corpses or coffins in a form that might give rise to new cases of smallpox is now extremely remote.

Unless there were a complete breakdown of health services, so that countermeasures could not be mounted, the occurrence of an accidental case of smallpox could be readily contained, as was apparent in the Birmingham outbreak. Even microbiological warfare with variola virus should not present a significant hazard, in terms of the re-establishment of smallpox as an endemic disease. Its nature would be quickly recognized and countermeasures could be taken, calling if necessary on the personnel and materials provided by WHO as part of the "insurance policy" (see Chapter 28).

CHAPTER 31

LESSONS AND BENEFITS

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INTRODUCTION

Smallpox is the first disease to have been eradicated by concerted and determined action on a global scale. This was not achieved, however, until more than 175 years after Edward Jenner's demonstration of the use of cowpox as a vaccine and his assertion that it was capable of eliminating smallpox from the earth. The vaccine virus had been promptly and widely distributed in the world, and vaccination was eagerly taken up as a protection against a universally feared disease. However, smallpox continued to spread as sustained control efforts were beyond the capacity of many government and health structures and vaccinations were frequently unsuccessful, especially in warm climates. Through the nineteenth century and the early part of the twentieth, tens of millions of persons were affected, of whom one-fifth or more died; no country was entirely spared. A heat-stable vaccine perfected in the 1920s helped to increase the efficacy of vaccination in the tropics, but it was difficult to produce and was not widely used.

As health systems improved and more extensive vaccination could be undertaken, the industrialized countries became free of endemic smallpox by the 1950s but frequent introductions of the disease from less fortunate countries obliged them to maintain costly national vaccination programmes and to endeavour, not wholly successfully, to protect themselves by compelling all travellers to be vaccinated. In most developing countries, few people were successfully vaccinated and smallpox was essentially uncontrolled.

A change in the approach to smallpox control was proposed in 1958 at the Eleventh World Health Assembly by a delegate of the USSR, who advocated that all countries should collaborate in a global eradication programme. This was unanimously approved by the Health Assembly the following year. At the time, 60% of the world's population lived in areas in which smallpox was endemic.

The next 7 years saw some improvement in the quality of vaccine and some countries did become free of smallpox, but the disease continued to be widely prevalent and epidemics were frequent.

In 1966, the government delegates to the Nineteenth World Health Assembly decided that increased resources were required and allocated special funds for the Intensified Smallpox Eradication Programme that was to begin on 1 January 1967. They proposed a goal of 10 years for the achievement of eradication. This was an optimistic goal, given that some 10–15 million cases were then occurring annually in 31 endemic countries or territories with a total population of more than 1000 million; that a century and a half of vaccination had yielded only modest results; that programmes would have to be conducted in most of the world's least developed countries; and that civil strife, famine and floods could be expected as recurring problems. Nevertheless, the last endemic case of smallpox occurred just 10 years, 9 months and 26 days after this programme began.

The rapidity with which smallpox was finally eradicated after so long a history of persistent transmission suggests that lessons may be derived from the experience of the Intensified Programme to benefit other initiatives in health and development. Most significant is the extraordinary achievement which was possible when countries throughout the world collaborated in the pursuit of a common aim, making use of the structures of an international organization and acting under its auspices. This made it possible for the necessary resources to be mobilized and applied to better effect, for improved methods of management and epidemiology to be introduced and widely applied, for vital modifications in strategy to be communicated quickly, and for new and often very simple techniques suited to a country's capacities and characteristics to be introduced promptly. In consequence, international confidence and accord were strengthened and a foundation was laid for other community-wide health programmes.

The smallpox eradication programme, however, cannot serve as a template for other disease control or eradication campaigns. Every disease has its own epidemiological characteristics and methods for its control which require strategies and tactics specific to it. Also, the approach taken to the eradication of smallpox differed considerably from country to country and was continually modified to capitalize on an evolving understanding of smallpox epidemiology and to deal with different local conditions. It is important also to note that smallpox had a number of features which greatly facilitated eradication. Most important is the fact that its severity and ability to spread in any part of the world commanded both the attention and the concern of health authorities everywhere. It had no known animal reservoir; there were no long-term carriers of the virus; and a single attack of the disease conferred essentially life-long immunity. The detection of cases was comparatively simple because the rash was so characteristic and persons with subclinical infections did not transmit the disease. Finally, a highly effective, easily administered and surprisingly heat-stable vaccine, conferring long-term protection, was available by the time the Intensified Programme started. Taken together, these characteristics are unique in relation to human infections. Indeed, when the goal of eradication from all countries of the world was decided upon, its feasibility in most of the industrialized countries and some of the developing ones had already been demonstrated.

The earliest successes of the Intensified Programme were recorded in western and central Africa, where it was quickly shown that smallpox spread less rapidly and less easily than most people had thought and that the prompt detection and immediate containment of outbreaks were vitally important—facts that were to have a profound influence elsewhere. Although the 21 countries concerned included some of the world's poorest and most heavily infected, 17 of them became free of smallpox within 2 years of the start of the programme in January 1967 and the last cases were discovered in June 1970. In Brazil, too, surprisingly rapid progress was made and endemic smallpox was eradicated from the Western Hemisphere in April 1971.

The provision of adequate supplies of potent freeze-dried vaccine and the introduction of the simple bifurcated needle had a remarkable impact on the incidence of smallpox in most countries, even those in which it was not possible to mount fully satisfactory programmes. This was especially notable in eastern and southern Africa where, by the end of 1971, smallpox had been eliminated from all but 3 countries. Meanwhile, well-executed programmes, in which the detection and

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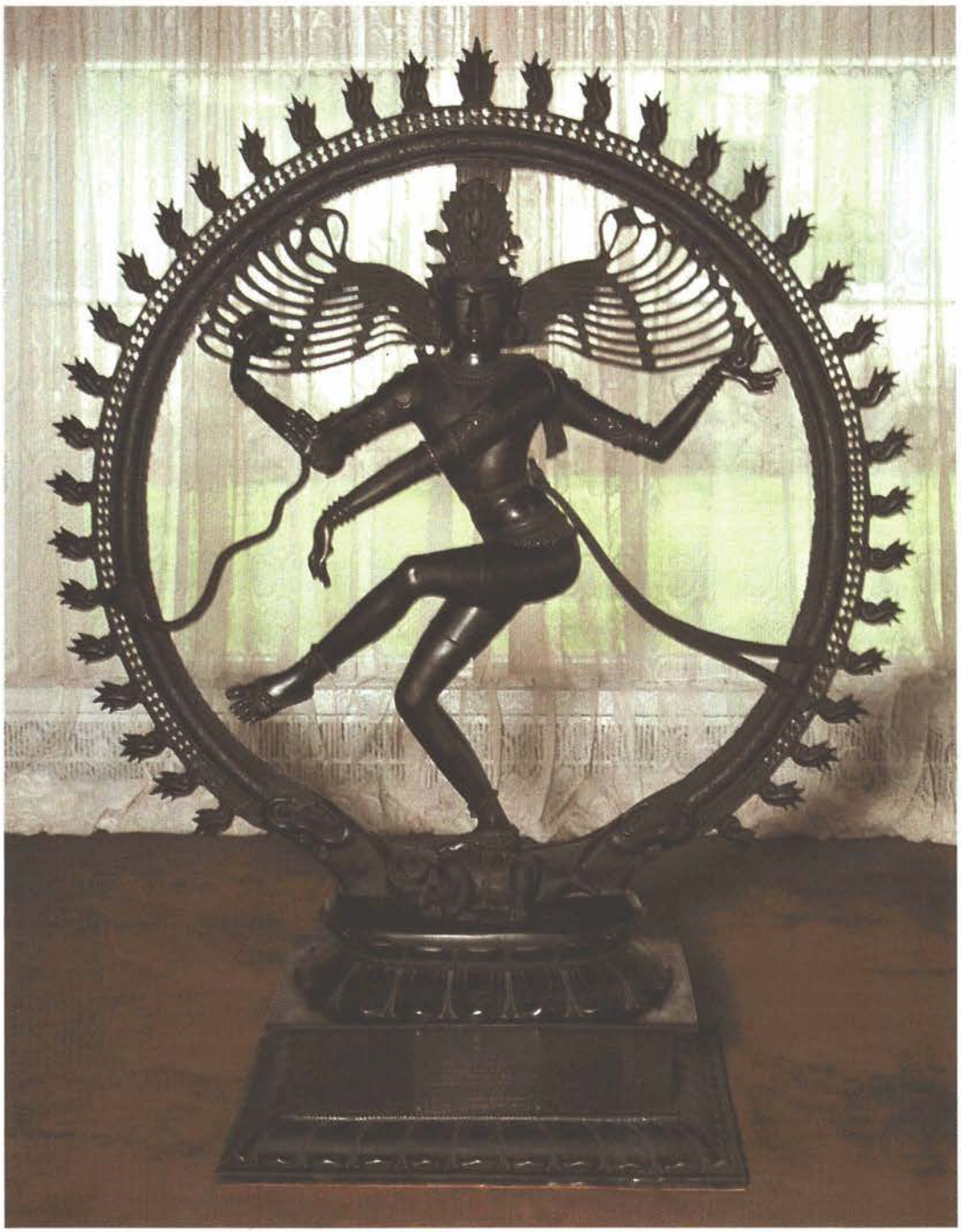
Plate 31.1. The Headquarters of the World Health Organization in Geneva, Switzerland.

WHO

Plate 31.2. First-day cover issued by the United Nations, commemorating the global eradication of smallpox. Variola virus virions as they appear under the electron microscope are shown on the stamps. A replica of the Winged Victory of Samothrace (on the left of the envelope) was presented to WHO when it received the Albert J. Lasker Special Award for Public Service from the Albert and Mary Lasker Foundation in recognition of the role the Organization played in eradicating smallpox.



WHO / J. GERMAIN

Plate 31.3. Dr Karan Singh, the Indian Minister of Health and Family Planning, presented the World Health Organization with this bronze statue of Nataraj on 15 August 1975, celebrating at once India's Independence Day and her freedom from smallpox. The statue is now in the Executive Board lounge at WHO Headquarters.

containment of outbreaks were an important feature, stopped transmission in East Pakistan (now Bangladesh) in 1970 and in Indonesia and Afghanistan in 1972.

Serious setbacks to the global programme occurred or were first confirmed in 1972. That year Bangladesh became reinfected with the return of vast numbers of refugees immediately after the civil war that had led to its independence; Botswana was swept by an epidemic as a result of introductions of the disease from South Africa; and it became known with certainty that Iran had become endemic in 1970 and Iraq in 1971. By late 1973, however, special campaigns had succeeded in eliminating smallpox from all the reinfected countries except Bangladesh.

In September 1973, greatly intensified campaigns began in the 5 remaining endemic countries: 4 in Asia (Bangladesh, India, Nepal and Pakistan) and 1 in Africa (Ethiopia). In the densely populated areas of Asia, new methods and extra resources were required to cope with smallpox among people who moved much about their country and among the large groups of persons displaced by natural disasters or civil strife. The employment of tens of thousands of health staff in ingeniously devised, well-supervised search and containment programmes made it possible to stop transmission in Pakistan in 1974 and in the other 3 countries in 1975.

Late in 1975, personnel and additional resources were shifted to Ethiopia, then the only country in which smallpox remained endemic. There, the milder form, variola minor, spread tenaciously across a vast and sparsely settled area in which civil strife was widespread and there were few roads or health services. Using many local volunteers and helicopters in yet another type of campaign, the smallpox eradication staff contained the last outbreak, in the Ogaden desert, in August 1976. However, civil war and the exodus of many refugees brought about a reintroduction of the disease into Somalia. Experienced staff and resources from many countries were mobilized to deal with this emergency, and the world's last naturally occurring outbreak took place on 26 October 1977.

Endemic smallpox had been eradicated but the health authorities of the world had to be completely confident of this fact if they were to forego the security—and the expense—of vaccination. Close surveillance and special searches had therefore to be conducted in many countries for at least 2 years after the last known case had occurred before international commissions appointed by WHO could be asked independently to verify the absence of smallpox. Finally, a WHO Global Commission undertook a variety of studies to satisfy itself that eradication had been achieved throughout the world, its conclusions being endorsed by the Thirty-third World Health Assembly in May 1980.

No two national eradication programmes were exactly alike, and all changed as they evolved, different elements and approaches contributing to the ultimate success. In this chapter, we try to identify the most important principles and lessons which appear to have a bearing on other community-wide health activities. Many of the conclusions are shared by other authors (Dutta et al., 1975; Foster, 1977; Sharma, 1980; Yekutiel, 1981; Hopkins, 1985; Jarrett, 1985), but differences are also apparent as each author has approached the question with a different experience and from a different point of view. Finally, we attempt the difficult task of assessing the costs and the benefits of the eradication of smallpox.

PRINCIPLES AND LESSONS

Political Commitment, Coordination and Implementation

For a world-wide programme against a disease to be successfully undertaken, all countries must agree to it and there must be a mechanism for coordinating and monitoring the work. The World Health Assembly provides the necessary and, indeed, the only forum in which global health policies can be agreed upon; and the World Health Organization alone has the requisite channels of communication with the national authorities through which their several programmes can be coordinated, with the support of the international scientific expertise upon which the Organization can draw. Both the Health Assembly and the World Health Organization were essential to the success of smallpox eradication.

The policy decision by the Twelfth World Health Assembly (1959) to undertake the global eradication of smallpox represented an important first step. Through the 1950s, most national governments and colonial adminis-

trations had conducted smallpox control programmes, some of which were very effective. If any disease were to be eradicated by such a widespread although uncoordinated effort, smallpox was the most likely one, given the threat it posed to all countries and the availability of an effective vaccine. However, the interest of national authorities in smallpox control waxed and waned with the varying incidence of the disease and as they became temporarily free of it or, on the contrary, were reinfected from abroad. A concerted and sustained initiative, supported by one or more bilateral assistance agencies, might have succeeded in eliminating smallpox from many countries but it is unlikely that it could have achieved world-wide eradication. Moreover, a scheme to certify that eradication had been accomplished would have carried little conviction without the credit and authority of an international agency which could mobilize respected scientists from throughout the world.

Some countries were encouraged by the decision in 1959 to begin or to intensify their own special programmes and some bilateral support was found, but 3 factors compromised the effort. The first was that the World Health Assembly did not back up its decision by the allocation of special funds, and WHO provided very few staff to coordinate or assist the national efforts and very few funds to help their work. In the majority of countries little action was taken and eradication was assigned a low degree of priority. Second was the fact that in Brazil, South Africa and some countries of eastern Africa, the prevalent form of smallpox was variola minor, which caused only mild illness and few deaths and therefore ranked low among the many other health problems. The third factor was that several large countries were not then Members of WHO. For them, the resolution of the Health Assembly had no direct bearing on their national policies and few of them provided information about the incidence of smallpox or the nature of their activities to control it.

The allocation by the Nineteenth World Health Assembly (1966) of special funds for smallpox eradication signalled a change in priorities. It served to stimulate national commitment to the idea of eradication and encouraged the backing of bilateral assistance agencies; it permitted the recruitment of additional WHO staff; and it provided additional resources for national programmes. The annual allocation of US$2.4 million was not large when compared to the overall need, and minuscule compared to the amounts being expended for the prevention of smallpox in the industrialized countries, but it was an important stimulus without which eradication could not have been achieved.

National support for global smallpox eradication, expressed as unanimous approval of the programme in the World Health Assembly, did not quickly take the form of effective national action, often owing to inertia though sometimes for lack of resources. WHO could not compel a Member State to meet the responsibilities to which it had pledged itself, but by the exercise of moral suasion it was eventually able to overcome reluctance on the part of national authorities. This required WHO staff to play an active role in advocating that eradication programmes should be started and sometimes meant a direct approach to heads of state or other senior national figures when officials at lower levels failed to respond. This encouragement of national programmes and the subsequent support of their work would not have been possible without a technical staff in WHO of sufficient size. From 1959 through 1966, there were at most 1 WHO medical officer in WHO Headquarters and 4 or 5 with field projects who were engaged specifically in smallpox eradication—too few, and with insufficient funds at their disposal, to have any significant impact. In theory, the WHO representatives who were resident in most countries in which smallpox was endemic might have stimulated the development of eradication programmes, but each was responsible for coordinating all the WHO-supported activities in a country and served as a technical resource for other health projects. Few had any particular experience of smallpox eradication or the time to devote to it. As additional funds became available, the number of WHO smallpox eradication programme staff the world over increased to 50 in 1967 and eventually to more than 100. Their professional expertise was to prove essential.

At first, many senior WHO and national staff had believed that management skills only were required. The needs, as they perceived them, were simple and straightforward: to procure sufficient vaccine and to organize vaccination programmes. They believed that generalist managers, rather than epidemiologists or other specialists, were sufficient for this task. It was apparent from

the beginning, however, that the challenge was far greater than the straightforward application of vaccine. It was necessary to adapt vaccination programmes to different administrative, socio-cultural and geographical situations and to devise mechanisms to monitor and assess the work, in terms not only of the numbers of vaccinations performed but but also of their effect on the incidence of smallpox. A better understanding of smallpox epidemiology was required in order to refine the strategies and tactics. Better methods for vaccine production were needed, as were improved instruments for vaccination. It was also important to determine with certainty that there was no natural reservoir of smallpox and to demonstrate that the clinically similar and virologically related disease, human monkeypox, was not a serious threat to the programme. Complementing the staff of physicians was a cadre of non-medical staff, termed "operations officers", who proved to be invaluable in dealing imaginatively with the complex logistics of programme implementation. This network of professional WHO staff, although small in number compared to the tens of thousands of national staff, facilitated the rapid communication of new information throughout the world and assisted in adapting and applying it to national programmes.

In summary, the commitment of the World Health Assembly to a programme of global smallpox eradication provided encouragement to national health authorities to undertake programmes in their countries, an encouragement strengthened by the demonstration in previous years and in a number of developing countries that eradication was practically feasible. However, more was required than good intent and expectation. Meaningful levels of national and international support were essential, as well as mechanisms to harmonize the many different ideas and plans of multilateral, bilateral and national organizations.

The Importance of a Special Programme

Smallpox eradication was conducted through a specifically targeted and time-limited special programme with funds allotted specially for it both in the WHO budget and in most national budgets, and with full-time technical staff assigned responsibility for its supervision. In this respect it may be regarded as the type of categorical programme the conduct of which remains a contentious issue of health policy, especially in developing countries (Vittachi, 1985). Yet, it made important contributions to the development of health services because, far from being separately or autonomously administered, it worked with and through the existing national health service structures and had to coordinate its activities with those of other programmes. The basic health services network, for instance, constituted the foundation of the disease-reporting structure, and in all countries this had to be greatly improved by training and supervision in order to become effective and to provide quickly the accurate information on which the containment of smallpox depended. Immunization programmes were strengthened in many countries as smallpox eradication teams undertook to provide other vaccines, such as BCG, measles, yellow fever and DPT, and assisted with the transport of personnel and supplies for other programmes. Some participation of the existing health staff in vaccination and in search and containment activities was required everywhere because of the small numbers engaged full-time in smallpox eradication. In consequence, many thousands of health staff received training in the execution of vaccination programmes and in field epidemiology; in many cases the only field supervision they received was provided in the course of their smallpox eradication work. A substantial number who now occupy senior positions in national and international organizations are successfully applying methods used for smallpox eradication in programmes against other diseases. These methods include the use of surveillance systems for management and assessment, sample survey techniques to measure performance, and the use of disease-recognition cards to help in case detection.

Experience in the programme demonstrates 3 principles of importance to health policy decisions: (1) the provision of disease control services which reach all persons in the community requires strategies and systems of management for which traditional health care delivery systems are ill-equipped; (2) special programmes to deal with health problems of general concern offer the advantage of attracting both resources and community support; and (3) the significant improvement in efficiency and supervision that can often be realized in special programmes may well

offset the additional costs they sometimes entail.

The delivery of community-wide services

Health officials in most countries have recognized that traditional health care systems—comprising a network of medical practitioners, health centres, and hospitals—have been designed fundamentally to provide therapeutic services for those who seek help and are ill-equipped to deliver preventive and other services which must reach all or most persons in a community. The limitation of traditional health care systems has been that only a proportion of the population, usually the better-educated, has taken the initiative to seek its services and only some of them have benefited from what preventive services have been offered. Few in the health care system have had the training that would enable them to design or implement programmes for the delivery of services to the whole of the population. Just as, in the 1950s and 1960s, most endemic countries assigned special teams to provide smallpox vaccination, so did they have special teams and programmes to deal with tuberculosis, yaws and malaria, for vector control, for family planning and so on.

The experience in national smallpox eradication programmes confirmed that the existing health care structures were inadequate to deal with community-wide programmes of disease control. Health centres, for example, were customarily directed by physicians or others whose training and preoccupation were with curative medicine, whose management skills were limited, who rarely left the health centres and whose work was seldom supervised. Few centres gave vaccinations of any type and, when they did, often used vaccine that was not properly stored or handled. The cases of smallpox that were seen were only occasionally reported and then usually with great delay; outbreaks were rarely contained. The hospitals performed even more poorly, the inadequacy or lack of isolation procedures actually serving in many instances to augment the transmission of smallpox; even the hospital personnel themselves were often unvaccinated. Travelling teams of smallpox eradication staff endeavoured to alter practices and procedures but only when the personnel of health centres and hospitals were trained and regularly supervised by smallpox eradication programme staff did the performance improve significantly.

It became apparent that in all countries there was a need for a specially dedicated and trained professional staff at all levels to decide and coordinate the strategy and tactics of the smallpox eradication programme and to modify these according to local needs, to develop reporting and surveillance systems, to undertake case-detection and containment measures, and to train local health staff in vaccination procedures and the proper preservation of vaccine. There was a need, too, to seek the support of village leaders and, through them, the acceptance and participation of the population. Such activities were alien to most traditional health care units.

The necessity of providing far more than curative care in order to meet the health needs of the community was recognized at the International Conference on Primary Health Care, held at Alma-Ata, USSR, in 1978. It identified primary health care as the key to this goal, being composed of a group of activities encompassing promotive, curative and rehabilitative services for all in the community.

Primary health care is often discussed as though all its activities could be pursued in a like manner, and indeed the skeletal structure of the traditional health care system can sometimes serve as the base for both preventive and curative services. As was apparent in the smallpox eradication programme, however, a different orientation and training of personnel are required for community-based programmes whose objectives are more broadly defined in terms of preventive and other disease control activities intended to reach all in the community. If directed by physicians with traditional training, the standards of the traditional service for the delivery of health care will usually be assessed by the level of training and skill of its practitioners, the quality and sophistication of its facilities and the numbers treated. In contrast, community-wide programmes—whether preventive (such as those for immunization or family planning), curative (such as those for oral rehydration or for the therapy of yaws or malaria), or a combination of the two—require that the standards of performance be assessed in terms of success in dealing with health problems in the community. Such programmes require active outreach through public education and persuasion to ensure their acceptance, the provision of services at a

site and time convenient to their clients as well as methods, such as surveillance, to measure the degree of success. Based on the experience in smallpox eradication, few traditional health care systems have been designed or their personnel equipped to handle both types of activity, and thus curative medicine has remained their dominant concern.

Attraction of resources and community support

Special-purpose programmes to achieve certain clear and specific objectives, usually within a finite period of time, have usually been better supported and financed by politicians and the public alike than have programmes, however laudable, whose health goals have been less explicitly defined. Thus, a programme to eradicate smallpox or to prevent poliomyelitis has had more appeal than one to develop the basic health services; indeed, almost without exception, public service organizations deal with particular diseases (e.g., poliomyelitis, tuberculosis or cystic fibrosis) or groups of diseases (e.g., cancer or lung diseases). Such programmes can serve broader objectives in the development of the health services, as did smallpox eradication, but support for health programmes that have lacked a categorical focus has often proved difficult to obtain.

Such special-purpose programmes are particularly important in public health because it is always more difficult to obtain a political commitment to and financial support for public health programmes than for those involving curative medical services. There are several reasons for this. First, political leaders are more readily persuaded to provide funds for curative services which, with their hospitals and health centres, are more tangible than a community-based programme. Secondly, the physicians who are most likely to be consulted regarding needs and priorities in health care are clinicians, who are more numerous and usually more influential than public health physicians; lacking a public health perspective, they tend to favour the development of clinical facilities which they will use. Thirdly, those who are the most disadvantaged and have the greatest need for community-based health services are usually the least influential politically. Thus, special-purpose public health programmes which can command attention provide an important balance to the traditional biases in allocation of health resources.

Special-purpose programmes are also associated with intensive publicity, which provides an opportunity to educate the population regarding the desirability of selected health interventions. For example, comparatively few people will voluntarily seek to be vaccinated, but more than 80% can usually be reached during the course of a well-publicized and well-executed mass campaign. As Jamison (1985) has pointed out, China's remarkable improvements in health over the past 30 years can be attributed in substantial measure to its special health campaigns, of which there have been 4 or 5 each year.

On a global scale, there is no better recent illustration of the potential for heightened support for community-based health programmes with specific objectives than WHO's Expanded Programme on Immunization, whose goal, established by the Thirtieth World Health Assembly in 1977 (resolution WHA30.53), is to provide 6 vaccine antigens to children throughout the world by 1990. This effort was augmented by UNICEF's Child Survival and Development Revolution and was subsequently endorsed in the United Nations (Mandl, 1985). International support of unprecendented magnitude was mobilized, national governments responded with special programmes and, as a result, levels of immunization coverage significantly increased in many countries.

Efficiency and supervision

Special programmes which involve the large-scale delivery of services permit economies to be realized and can facilitate better management of supplies and equipment than is possible when services are provided only in established health centres or practitioners' offices. Immunization programmes are a case in point. The cost of a dose of vaccine in multiple-dose containers is far less than that of the same dose individually packaged. To take full advantage of this, however, all or most of the contents of the larger container must be used at once, because vaccines deteriorate rapidly after the vial is opened; this is most easily accomplished in a large-scale campaign in which large numbers of people are vaccinated each day. Another but more difficult approach is to assemble large numbers of children at clinics on special vaccination days.

The efficient use of vaccine is also more readily achieved when a few vaccinators

perform many vaccinations than when many health centre staff each perform a few. Throughout the course of the smallpox eradication programme, there were recurring problems in ensuring proper vaccination technique and the proper sterilization of instruments by hospitals and health centres. Despite frequent visits by supervisory smallpox staff, many health centres in all countries regularly stored reconstituted vaccine far longer than the 1 day that was prescribed and ignored or were unable to cope with refrigeration failures. Although similar problems affected vaccination teams, it proved far easier to supervise, say, 10–25 vaccination teams than 100–250 health centres.

Definition of Objectives and Goals

From 1967, the most important difference between the Intensified Smallpox Eradication Programme and the previous efforts was that the strategy and tactics were decided in terms of a clear ultimate objective—a nil incidence of smallpox. Although this objective is implicit in any eradication programme, progress before 1967 had been measured primarily by the numbers of vaccinations performed; the reporting of cases was considered so deficient as to be meaningless (WHO Expert Committee on Smallpox, 1964) but nothing had been done to improve its quality. Focusing on the objective of a nil incidence meant that the reporting of cases had to be improved and surveillance systems and field epidemiology developed. New methods were devised for discovering cases and containing outbreaks; resources were allocated in such a way as to provide for particularly intensive efforts where the incidence was highest, at times when transmission was most susceptible to interruption and in places where the risk of spread was greatest. In effect, this approach served to blend management with epidemiology.

Logic suggests that any disease control programme should provide continuous measurements of its impact on incidence and that these in turn should dictate changes in strategy and tactics. In fact, this is seldom the case even today. Most authorities ignore such information or dismiss efforts to obtain the data as being too difficult. Instead, progress is assessed in terms of activity, such as the numbers of vaccinations performed or of patients treated. Several countries in the early 1960s reported with satisfaction that they had vaccinated half or more of their population against smallpox each year, yet the incidence remained high owing to the use of poor vaccine and to lack of supervision. This clear indication that something was amiss with the management of the programme or the efficacy of the vaccine was ignored, however.

Although progress in the Intensified Programme was gauged primarily by the reduction of smallpox incidence, subordinate programme goals were also established in each country and area. They closely followed the principles for good management enunciated by Austin (1979), being specific, measurable, realistic and dynamic. For example, mass vaccination campaigns were expected to result in more than 80% of the population in each area having a vaccination scar. Assessment teams could easily determine the proportion of the population with a scar and, as experience showed, this goal could readily be achieved with a reasonably effective campaign. As programmes improved, this target was made more rigorous, it being required that 80% of those under 15 years old and sometimes 80% of those under 5 should have a vaccination scar. Although more difficult, these standards were not beyond attainment. For successful primary vaccination, take-rates of 95% or more were established as the standard, one which could be readily measured and was tolerant of error since rates of 99% and more were customary under optimal conditions.

From 1974, standards were also established for surveillance and containment. They established as goals that 75% of outbreaks should be discovered within 2 weeks of the onset of the first case, that containment of the outbreak should begin within 48 hours of its discovery and that no new cases should occur more than 17 days after containment had begun. As the incidence of smallpox decreased or ceased, other standards for the measurement of performance were developed which related to the population's knowledge of a reward for reporting cases and the completeness of reporting of other diseases, such as chickenpox.

The various standards were of the greatest value when the data were promptly collected, analysed and used as management guides for programme action. The knowledge by those collecting the information that their data were being promptly put to use contributed

greatly to the development of the system and to better performance. There was a limit, however, to the number of standards that could be effectively employed. This became evident during the concluding phases of global eradication as more standards were adopted and their stringency was increased: a growing volume of data accumulated, only a portion of which could be satisfactorily analysed and interpreted for use. It was apparent that a few indicators of overall performance, closely followed, were more valuable than a broad spectrum of indicators expressing the measure of many different aspects of programme execution.

Quality Control

Methods to ensure that smallpox vaccine was potent at the time of its use, that vaccination coverage met the expected goals, and that progress was being made in diminishing smallpox incidence all represented forms of quality control. Before 1967, their application was infrequent. In both industrialized and developing countries, vaccines, even at the time of manufacture, often failed to meet the accepted international standards; few independent national testing centres monitored vaccine quality; and few health service staff examined the vaccinated after one week to determine whether their vaccinations had been successful. In many countries, large numbers of vaccinations were regularly reported but seldom was there confirmation of this by sample survey to check vaccination scars. It was known that the cases of smallpox that were reported represented only a fraction of the total but even these data were seldom reviewed to determine epidemiological trends or patterns of incidence.

The evident disinterest in quality control which characterized smallpox control programmes before 1967 is difficult to understand, but in fact it typifies large segments of current public health and medical practice. In many countries, for example, biological and pharmaceutical products are accepted and used with little assurance of their potency or purity and with little confidence that they have been properly refrigerated. Even the most elementary measurement systems, such as the enumeration of deaths by cause and the incidence of important diseases, are manifestly deficient. Where systems exist for the routine collection of information, the data, more often than not, are consigned to statistical reports. The fact that the concept of surveillance, although simple in principle, proved so difficult to apply, reflected the lack of experience with measurement throughout the health field and, indeed, the lack of programme goals which would encourage such measurement.

Programme Management

Multinational, cooperative health programmes are inevitably difficult to manage, given the realities of national sovereignty and the intrinsic problems of international organizations. The smallpox eradication programme could not operate as a monolithic structure, like a military command; rather, it was obliged to function in a collegial structure of many independent national programmes, each with its own administrative traditions and socio-cultural patterns, and utilizing resources from many different sources. It was a programme in which WHO, the coordinating organization, provided only a small proportion of the resources and had no authority with respect to national programmes other than that of moral suasion. Authority and responsibility within WHO itself were highly decentralized, each of its 6 regional offices enjoying a substantial degree of autonomy. With its functions and its structures at the time, the Organization was better suited to the implementation of local or regional programmes than to the execution of a world-wide programme which required international mobilization and the selective allocation and re-allocation of resources on a global basis.

Other global health programmes are confronted with similar challenges today. An effort is therefore made here to identify factors in management which contributed to the eradication of smallpox and which might facilitate more effective and better coordinated programmes of other types.

The network of professional staff

Because a hierarchical structure of international and national staff was not possible, other mechanisms had to be found to coordinate planning and to ensure continuity in the execution of the work, to control the quality of vaccines and of performance alike, and to

assess and redirect the programme as it evolved. Within WHO itself, the successful accomplishment of these tasks depended primarily on the recruitment of capable professional staff who could be given substantial latitude to make decisions, who could be assured of the funds, manpower and administrative support they needed, and who could be provided with leadership by example and exhortation rather than by directive. In the broader reaches of the programme much depended on the extent to which continuing close communication could be maintained between the national and the international staff, on their degree of mutual respect, and on the level of their common understanding of problems and needs.

A unit at WHO Headquarters with overall responsibility and accountability for all activities related to the programme proved to be essential. At first, the responsibility for a number of activities directly pertaining to smallpox eradication was scattered among a variety of units. The testing of smallpox vaccine and the development of its production were the concern of one small unit which had to deal with the entire field of biological products; notifications of smallpox cases were received by the units concerned with the application of the International Health Regulations and with the compilation of international health statistics; and yet another unit, concerned with virus diseases, dealt with smallpox research. The Smallpox Eradication unit gradually assumed the responsibility for all the activities that concerned the programme and they subsequently became more effective and more responsive to the programme's needs.

More rapid progress might have been possible if, from the beginning, there had been special staff to handle two other activities—public information and soliciting contributions from donors. There was a need to publicize widely what was being done, and where and how, in order to encourage national authorities and the participating staff and to recruit support from donors. WHO's public information office did what it could but was unable adequately to meet this need as it was small and had to serve the Organization's many other interests and programmes. Use of the *Weekly epidemiological record* to publish a full and candid account of progress and problems in the programme at intervals of 2 or 3 weeks served well to inform the public health community, but it was not especially helpful in stimulating coverage by the mass media for the information of a broader public. A marked change occurred in 1977, when a full-time public information officer joined the smallpox eradication programme. His efforts proved vital to fostering public confidence that eradication had been achieved and that vaccination could be stopped. There were no professional staff in WHO, however, whose full-time responsibility it was to solicit voluntary contributions even though two-thirds of all international funds for the programme were expected to be provided from this source. The staff of the smallpox eradication programme undertook to raise these funds as best they could but they lacked the expertise, the necessary political contacts and the time, and their success was limited.

The Smallpox Eradication unit at WHO Headquarters provided a central point of contact for those outside the programme, whether scientists in research or vaccine production laboratories, potential donors, possible candidates for service, or the media. Because the unit needed to keep abreast of the latest developments to disseminate current technical information about the programme as widely as possible, frequent and regular communication between the scientific and public health communities and the staff of the unit was encouraged. This facilitated the rapid application in practice of new developments and benefited other operations as well.

A counterpart professional group of at least 2 or 3 persons in each of the 4 WHO regions in which smallpox was endemic would have been invaluable, particularly because of WHO's decentralized structure, but, although this was strongly encouraged, it was implemented in only 1 region. Consequently functions that might more logically have devolved upon the regional offices of WHO often had to be undertaken from Headquarters; national programmes were not always adequately supported or monitored; and the global coordination of activities was less satisfactory than it might have been.

For national programmes, an accountable and responsible professional person, preferably appointed to deal exclusively with smallpox eradication, was considered essential by WHO as a locus of contact and for the planning and implementation of the programmes. Each country was therefore requested to designate a specific person to be responsible for smallpox eradication rather than simply an office or a section of the health

ministry. This proved effective except in countries where officials were frequently transferred. However, 3 functions which were customarily the responsibility of parts of the ministry not directly concerned with disease control often presented special problems: case reporting, quality control of vaccine, and public education.

The national notification of cases was often the responsibility of a statistical unit which mechanically recorded such data as were received, showed little concern with the completeness of notifications and was not responsible for initiating action based on the reports received or compiled. Such systems seldom improved unless the smallpox eradication officer assumed the responsibility for the notifications of smallpox cases and used the data for monitoring the programme and allocating resources. This assumption of responsibility, however, often did not occur until many months or years after programmes began.

The quality control of smallpox vaccine was a problem in most countries which produced their own vaccine. Usually they had no national control laboratories and the production laboratories themselves were the ultimate arbiters of quality. Although it was WHO policy to have a WHO collaborating centre test all vaccines used in the programme, the laboratory directors often opposed this and sometimes refused to submit samples. The national smallpox eradication programme officers had no authority to enforce the policy and so it was frequently necessary for senior WHO staff to intervene with higher-level government officials. Compliance, however, was seldom easily achieved, and in a few countries substandard vaccines continued to be used even though the problem was known and recognized.

Responsibility for health education was usually assigned to a special unit in the ministry of health, but such units were seldom either adequately staffed or especially able or imaginative. Few contributed significantly to smallpox eradication campaigns, most educational efforts being mounted by regional and local smallpox programme personnel who pragmatically developed materials as required.

Overall, the basically collegial management of the programme functioned surprisingly well, its principal handicap being the lack of adequate numbers of senior staff at WHO Headquarters and in the regional offices, in national programme offices and in states or provinces. Paradoxically, national governments were reluctant to provide one or a few additional senior supervisory staff, even when available, although they were almost always prepared to add tens, hundreds or even thousands of vaccinators. In one of the largest countries, for instance, the national programme directorate consisted until 1972 of only 1 professional person, and in one of WHO's regional offices smallpox eradication was the part-time responsibility of a medical officer who had to deal with all communicable diseases.

Personnel recruitment and training

The competence, motivation and experience of the staff ultimately govern the success of all programmes and this was unquestionably the case with smallpox eradication. Within WHO, considerable time was required to assemble the professional staff that was needed. Except for staff at Headquarters, recruitment was the *de facto* responsibility of the regional offices. Other factors of selection sometimes outweighed those of professional competence and motivation, and the smallpox eradication staff at Headquarters were, at first, seldom consulted by the regional offices about personnel decisions. Performance was not always closely monitored and contracts were sometimes renewed irrespective of performance, or personnel who proved unsatisfactory in one post might be transferred to another that could be as crucial to the programme as their previous position. However, increasing numbers of competent staff were recruited to WHO as special efforts were made by Headquarters to identify qualified candidates through personal contacts with an informal network of reputable epidemiologists, and applications were encouraged from staff who had performed well in national programmes.

The quality of national programme leadership was initially no less uneven; as the programme progressed, however, and eradication appeared more attainable, national officials increasingly assigned direction to their more able staff, many of whom had previously demonstrated their competence in field operations. Contrary to a widely held view, most countries had more than enough competent staff who could assume positions of leadership, even if many of them lacked practical experience in management because

their supervisors had been unwilling or unable to delegate authority and accountability.

A common understanding by all the senior national and international staff of the principles underlying the programme, of its essential components, and of the more important measures of progress was as crucial to success as the quality of the staff, for on it depended the ability of the programme directors to introduce effective innovations and to adapt their programmes to the prevailing circumstances. The *Handbook for Smallpox Eradication Programmes in Endemic Areas* (SE/67.5 Rev.1), surveillance reports, national and intercountry meetings, and personal visits all helped to accomplish this. The experience in the programme in western and central Africa suggests that special training programmes of perhaps 2–4 weeks' duration for all newly assigned international and senior national staff would have been equally useful elsewhere. However, a lack of appreciation by the regional offices of the need for such courses and a dearth of senior personnel to conduct them precluded their development until 1974. At that time, the intensification of the programmes in India and Bangladesh brought in sufficient additional WHO staff and consultants and specially recruited national epidemiologists to permit training programmes to be conducted in each of the remaining endemic countries.

National smallpox eradication programmes were usually staffed by persons already engaged in smallpox control and others who were reassigned from other programmes. Most countries had many more health staff than programmes with the resources to support them and their work. Given 1–2 weeks of practical field training for smallpox eradication, a steady flow of the supplies and equipment they needed and good field supervision, most performed competently and with dedication. The quality and the nature of the supervision they received were of vital importance. The best results were obtained where WHO, national, and state or provincial supervisory staff travelled frequently into the field to review activities, to resolve problems and to work with the field staff on the solution of their problems. Monthly or fortnightly meetings at which the field staff and supervisors from different areas met to discuss progress and problems and to compare results also proved valuable.

Not only was smallpox a disease with which the ordinary villager was familiar and that he could easily recognize, though he might confuse it with chickenpox, but it also became evident early in the programme that the villagers and their leaders, if properly approached, were usually willing—indeed, eager—to cooperate in organizing vaccination programmes and in detecting cases. From 1973, when programmes in the remaining endemic countries were intensified, many of them were recruited and trained for part-time work in these activities. Their performance, as that of other field staff, was directly proportional to the clarity of the direction provided and the quality of the supervision they received.

In brief, it was clear that comparatively few, strongly motivated and knowledgeable professionals could organize and effectively mobilize large numbers of persons and that in most countries they could count on the eager support of the health staff and the general population alike. The limiting factor was the inadequate number of motivated and knowledgeable leaders, largely because too few were recruited, trained and assigned to responsible positions.

Financial and other resources

A deficiency of resources was a continual problem, which seriously jeopardized the international effort. Despite the importance of global smallpox eradication for all countries, support for the programme was barely adequate to sustain it, even during the last months before transmission was stopped. In large part, this was due to scepticism during the early years of the programme about the feasibility of eradicating a disease. Global malaria eradication had required and received substantial resources, but it was increasingly recognized to be unattainable. In consequence, disappointed bilateral donors and organizations of the United Nations system gradually withdrew support and many declined to provide more than token help for yet another eradication campaign. Such efforts as were made to inform potential donors of the progress being made in smallpox eradication and of the programme's needs proved inadequate until 1974. An intensified, well-publicized campaign had by then begun to stop transmission in the 5 remaining endemic countries as quickly as possible, before natural or man-made catastrophes could thwart the effort. When it became evident that additional resources were indispensable, special

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Plate 31.4. Even Snoopy, the well-known cartoon character, supported smallpox eradication. He was never vaccinated, however. (Drawn by Charles Schulz, 1976.)

funds were made available by WHO and large contributions were received from Sweden and later from several other donors. These made possible the successful, large-scale programmes in Asia, but until 1976 they were insufficient to strengthen adequately the programmes in Ethiopia and Somalia. After the last case occurred in 1977, but long before the necessary work of certifying that eradication had been achieved was completed, support for the programme waned again.

Obtaining sufficient resources in the endemic countries often proved as difficult as obtaining international contributions. Although few countries had to provide significantly more money for smallpox eradication than for their previous smallpox control work, their health budgets were small and competing needs were many. To obtain adequate resources, special appeals to national leaders were frequently required. When a nil incidence was reached and the immediate threat of smallpox was removed, however, there was a strong incentive to allocate the men, money and materials to the control of other diseases; consequently, support diminished rapidly and resources to permit certification activities were seldom more than barely adequate.

Several requirements need to be borne in mind when there is a considerable dependence on voluntary donations of money or materials from different sources: (1) quality control of donated items; (2) standardization of supplies; and (3) availability of discretionary funds.

Donations in kind to the smallpox eradication programme were primarily gifts of vaccine, which was tested by WHO collaborating laboratories to be certain that it met the accepted international standards. Although it had originally been thought that vaccine from well-established laboratories in industrialized countries would not need to be tested, it was soon discovered that some of it did not meet the standards. It was found that many governments licensed producers to distribute vaccine which had been found acceptable only by tests conducted by the producer's own laboratory, and that the least competent producers were the least conscientious in vaccine testing and sometimes certified substandard batches. As a result of these findings, a number of countries were prompted to establish national vaccine control laboratories for the first time. The quality of vaccine subsequently improved significantly, but even then occasional batches of substandard vaccine were submitted for donation.

Standardization of equipment and supplies was especially important for items that required spare parts or knowledgeable mechanics for their maintenance. For vehicles and motor cycles, the most commonly provided articles, it was best to provide models already in general use in a country. The provision of unfamiliar products meant that stockpiles of spare parts had to be created and mechanics had to be specially trained. This could be done reasonably economically on the scale that obtained in the larger countries, but it gave rise to considerable problems in smaller countries. In all countries, however, the provision of only a few vehicles or motor cycles of unfamiliar manufacture usually proved to be more of a problem than a benefit. Standardization with regard to vaccine was also important. At first, vials from different manufacturers contained amounts ranging from 15 to 500 doses (0.15–5.00 ml) of vaccine, but this complicated programme planning and confused the vaccinators; efforts were therefore made to standardize all vials of vaccine so that

they contained 0.25 ml when reconstituted. Package inserts (printed forms detailing uses and contraindications) accompanying the vaccine also proved to be a problem because each country had its own policies regarding the age for and contraindications to vaccination. Eventually, however, all producers were persuaded to use a specially prepared WHO package insert which corresponded to global vaccination policies.

Finally, it is important to note that, for a programme financed principally by voluntary contributions, it was essential to have some unrestricted funds which could be used for any necessary purpose and in any country. Most donations were restricted for use in a single country or were received as contributions in kind; only a small proportion of them were received in cash and without limitations on their use. Fortunately, funds were available under the WHO regular budget to meet programme needs for which provision was not otherwise made. In western and central Africa, for example, the USA provided for all except what were known as "local costs" (costs of petrol, vehicle repair and *per diem* allowances for the teams), which its national policy prevented it from meeting; these costs were covered by WHO. There and elsewhere the sums required were small in comparison with the totals involved, but without discretionary funds most of the programmes would not have been able to operate. Likewise, although almost all the vaccine not produced locally was provided as contributions in kind, discretionary funds were needed for the purchase of vaccination instruments and for the printing of package inserts.

Logistics

Whether a programme functioned or failed depended upon the availability of vaccines, vaccination instruments, vehicles and other supplies. Without them, programmes stopped, the momentum was lost, smallpox spread, and morale fell quickly. It was not always easy to ensure that these items were available as needed, since the demand for them fluctuated as a result of natural and man-made emergencies, unexpected epidemics and a host of other factors. The WHO smallpox eradication programme took an active part in dealing with such problems, acting in an operational capacity rather than restricting itself to the advisory technical role that was more customary in many international programmes. This proved helpful in countless circumstances. Being in frequent contact with national and WHO programme staff, the Smallpox Eradication unit could sometimes anticipate problems and take preparatory action and was able to evaluate requests and to respond quickly. An emergency reserve of vaccine and vaccination instruments was created which permitted these to be distributed within 48 hours of a request being received; supplies and equipment could occasionally be diverted from one country to another; and special funds were sometimes provided for emergency procurement of equipment or to pay for special consultants.

The most intractable problem, and one that was never fully solved, was the supply of vehicles. Most health ministries were short of roadworthy transport and were usually unable to provide for emergency requirements. For vehicles of foreign manufacture there was usually a delay of 12–18 months between the submission of a purchase order and their delivery but it was often impossible to gauge the need for them more than 3–6 months in advance. The difficulty was resolved in some countries by purchasing locally manufactured or assembled vehicles and in others by the local purchase of already-imported vehicles, although this was usually more costly; in some instances, special workshops were established to repair and maintain the often large fleet of unroadworthy vehicles. Better results would have been obtained if it had been possible to procure a reserve fleet of new vehicles which could be dispatched quickly when needed, and if more efforts and resources had been directed to the development or improvement of national vehicle maintenance and repair facilities.

The dispensing of and accounting for funds and the uses to which they could be put were a constant, often formidable administrative problem. In many endemic countries, small *per diem* allowances and long delays in payment all but precluded travel by the national field staff; allowances for petrol often permitted only a few days of vehicle operation each month; budgets for vehicle maintenance and repair were small; and there was often no provision for the disbursement of funds for exceptional needs such as the establishment of facilities for the isolation of patients or the payment of a reward for reporting cases. These and similar fiscal problems were largely resolved by the use of WHO funds to meet the "local costs" mentioned above. Their use was

facilitated by establishing imprest accounts, which were an advance made to WHO advisers and senior national staff, for which they had to account before a further advance was made. The availability of ready cash in this way permitted action to be taken expeditiously and eased the work in the field. Implementation of the system was not without problems, however. For example, in many areas illiteracy made it difficult to obtain the receipts which a proper accounting called for, and in all programmes there were a host of questions as to what constituted proper expenditure. The propriety might be questioned, for instance, of making small payments to smallpox-afflicted beggar families in India to ensure that they remained in isolation. Without the sympathetic and flexible administrative support provided by WHO, satisfactory solutions would seldom have been found.

Operational tactics and strategy

An important principle underlying the operation of the smallpox eradication programme as a whole was that the administrative structure and pattern of operations of each national programme should be integrated as well as possible into the health and sociocultural setting of the country concerned. This differed from the operational strategy in malaria eradication, which called for a separate malaria service and laid down detailed administrative responsibilities and functions for personnel at every level. For smallpox eradication, the operational objective was broadly identified: the ultimate goal was a nil incidence of smallpox, to be confirmed by an adequate surveillance programme. To achieve this, a two-part programme was stipulated. First, a vaccination campaign was recommended to ensure a level of immunity among the population as a whole high enough to reduce the incidence of smallpox substantially; secondly, a surveillance programme was to be established to ensure prompt reporting of cases from all health facilities, to permit the investigation and containment of outbreaks and to analyse patterns of occurrence of smallpox so that corrective measures could be taken in both vaccination and surveillance activities.

Programmes were expected to be designed locally by the national staff and their WHO counterparts working in collaboration and to evolve and change with time in the light of experience. Consequently, programmes differed greatly from country to country and from time to time. The role of the WHO staff assigned to the countries likewise differed somewhat from one country to another. The most effective were those who served as working counterparts and took an active role in field operations. Those who assumed the more traditional role of passive technical advisers and rarely travelled outside the capital city were encouraged to leave the programme. As working counterparts, WHO staff with prior experience in other smallpox eradication programmes transmitted confidence in the feasibility of eradication and were better able to introduce new methods; they frequently served to provide continuity and sustain momentum in programmes when the national leadership changed; and it was sometimes easier for them than for their national counterparts to approach the more senior health officials in the country to seek additional support or changes in policy.

Given this operational strategy, the WHO smallpox eradication staff in Geneva viewed as their first priority a duty to anticipate and to be fully responsive to national programme needs and to provide all possible support to them. An immediate response to requests for resources or advice, continuing communication regarding progress and developments, and frequent contact through visits and meetings were essential elements. In consequence, those who served with the smallpox eradication programme, whether as national officials or as WHO staff or consultants, identified as much with international as with national goals; they related closely to each other; and they sustained a remarkably high level of morale despite incredibly arduous working conditions. Although a pattern of programme management such as this would appear only logical, surprisingly few multinational health programmes currently operate with this philosophy.

Global strategy and priorities were regularly discussed and decided at meetings with regional and national advisers and national programme staff. Forums such as these were valuable as it was in the course of executing national programmes that the most important observations were made, as a result of which significant changes in strategy and tactics were introduced. These international meetings provided opportunities for critical discussion of the experiences communicated,

for a comparison of observations, and for the charting of new directions.

The target of a nil incidence of smallpox—the completion of a finite task—undoubtedly played a role in motivating staff and sustaining interest. There are few health programmes which have such a clearly definable end-point. However, comparable levels of achievement, interest and morale in other programmes should be possible where specific goals are clearly identified, where progress is regularly monitored and where the programme staff are fully supported and encouraged in their efforts.

Research

The importance of the problem-oriented applied and basic research that was conducted throughout the course of the smallpox eradication programme cannot be too emphatically stated. The nature and extent of the research agenda could not at first be fully elaborated or foreseen. The most explicit question when the programme began was whether there was a natural reservoir of variola virus which could thwart the objective of eradication. Beyond this, there was the belief that studies conducted during the execution of programmes could do much to elucidate the epidemiology of the disease and to benefit programme implementation. There was, moreover, the belief that the potential of the tools and methods already available could be further developed to permit the task to be achieved faster and more efficiently.

What was not anticipated at the inception of the programme was the extent to which changes would occur in programme strategy and tactics and in the understanding of the epidemiology and virology of smallpox and other poxviruses. Contributions to these changes were made in a range of disciplines, extending from basic molecular biology to applied technology and the social sciences. The research agenda did not, however, unfold spontaneously. Smallpox eradication programme staff and consultants met regularly to discuss developments and needs. Many staff had to be encouraged and sometimes prodded to explore important questions. Substantial time and effort were expended in editing and preparing for publication many of the papers which were eventually distributed.

The fact that most research was undertaken during and in the context of the field work in order to answer practical questions or to resolve apparent paradoxes provided an unusual impetus to the research effort. Moreover, the interaction of research and programme execution permitted the prompt practical application of many of the findings.

The lesson for other disease control programmes seems evident. However, even today, despite countless discussions about the importance of research for smallpox eradication, other problems of importance to the developing countries receive little research support. Research in applied technology and the social sciences is notably neglected and the potential offered by modern molecular biology has barely begun to be realized. For health programmes in the developing countries, research is neither an academic luxury nor merely an interesting intellectual exercise, as has sometimes been suggested. It is a necessity for the successful prosecution of disease control and was inherent in the achievement of the goal of smallpox eradication.

Certification

A feature peculiar to smallpox eradication was that, once it had been achieved, health officials throughout the world—and the general public—all had to be sufficiently confident of the fact that the disease had been eradicated everywhere for them to abandon the practice of vaccination. To instil the necessary conviction, special certification activities were required; they are not without relevance to other situations in which one country's policy is shaped by the health conditions in other countries.

Fostering the required confidence presented difficulties at many levels. National authorities everywhere recognized that the reporting of infectious diseases was deficient in all countries and that in certain circumstances some governments suppressed information about known cases of smallpox (see Chapters 22 and 23). Within countries, smallpox vaccination, one of the oldest public health measures, was a well-established practice, not lightly to be discarded by those responsible for their country's health. The general population of the endemic countries readily recognized smallpox, and in many cultures it was so familiar as to be considered an inevitable occurrence of normal life. Continual efforts were made by the smallpox

eradication programme to publicize widely and in detail, both in the scientific and the general press, what was being accomplished and how. Accounts of the work appeared in WHO's *Weekly epidemiological record*; comprehensive summaries were prepared each year for the World Health Assembly and the Executive Board of WHO; numerous scientific papers were published; and coverage in the public media was actively solicited. These efforts intensified as the goal of eradication approached and was finally reached. Although they were partly successful in convincing many persons that the programme had been well conducted and that WHO and national officials spoke with justified confidence of the accomplishment, more was required.

In 1971, the decision was made to appoint independent international commissions of recognized scientists to visit each country in the endemic areas 2 years or more after the occurrence of the last known case so that they might satisfy themselves that the measures taken by the programme would have detected smallpox had it been present. If they were not satisfied, they were directed to recommend additional measures which should be taken. Such visits were arranged only when WHO and national staff were themselves confident that smallpox had been eradicated from an area and that the fact could be documented. Confidence in the process was enhanced when most countries followed a precedent set by Indonesia during the visit of the second of the commissions (early in 1974), when the members of the commission were informed that they could go anywhere they wished, that they could have access to any records they wanted and that they could question anyone about any matter pertaining to smallpox and the eradication programme (see Chapter 13). The first of the international commissions was convened in 1973; altogether, 22 commissions visited 63 different countries (see Chapters 24–27).

There were a number of salutary features of this approach which deserve mention. First, it required each country to prepare a special report setting forth the activities and the evidence which documented the absence of smallpox; this requirement stimulated national officials to support smallpox surveillance programmes after the last case had occurred and when the inclination was strong to divert resources prematurely to other needs. Secondly, wider knowledge of the nature of the programme and confidence in its success were gained by involving in the commissions scientists of many different nationalities, including those who were most sceptical. Thirdly, when each commission reached a decision that eradication had been achieved, important opportunities were presented to publicize the fact nationally and internationally.

A global commission, composed of 22 scientists from 20 countries and assisted by 9 advisers from 7 countries, surveyed the status of the programme from a world-wide perspective and recommended other activities which they believed were needed for them to be confident that eradication had been achieved. Although some activities involved special studies in areas and countries to which access by international staff had been limited, all were completed or satisfactory alternative measures devised and conducted.

Certification of smallpox eradication was valuable and necessary in giving the world community confidence in the achievement. Like the eradication programme itself, it was designed specifically to meet this need and cannot serve as a template to be applied to other questions in which mutual confidence among nations is essential for deciding sound policy. However, problems arising from national doubts about the status of conditions in other countries have arisen in the past and can be expected in the future. Such problems have included those pertaining to the acquired immunodeficiency syndrome (AIDS) and cholera, as well as natural and man-made environmental contamination involving chemicals and nuclear materials. In such circumstances, certain of the principles of the certification programme have applicability—specifically, assessment of the problem in question under the auspices of an international organization, the use of respected scientists of different nationalities who are requested to be critical in judgement, and open publication of their observations and conclusions.

COSTS AND BENEFITS

The eradication of smallpox marked the end of the pain and suffering of its victims who, as recently as 1967, are estimated to have numbered 10–15 million each year and among whom probably 1.5–2 million died. It marked the end of the severe disfigurement, blindness and other disabling conditions

among those who survived. It meant that all countries could utilize their smallpox hospitals and wards for other health purposes, that they could stop vaccination programmes and that travellers would no longer need to present vaccination certificates attesting that they had been successfully vaccinated.

The existence of smallpox had important financial implications for all countries. In 1967, all countries were expending substantial funds either to control smallpox and to care for its victims, as was the case in the endemic countries, or to vaccinate and operate quarantine programmes to prevent the disease from being imported, as was the case in countries which were free of endemic smallpox. The expenditure of considerably greater sums for further therapeutic or quarantine services would have accomplished little. However, modest additional expenditures for the prevention of smallpox made a dramatic difference. For the entire global smallpox eradication programme, the annual costs, on average, amounted to only US$23 million over the 13-year period, 1967–1979, a sum which includes both national costs and international contributions.

The benefits to all countries of eradicating smallpox would appear so great and so clear that it is difficult to understand why there were problems in obtaining the requisite resources and political commitment. In part, this reflects the fact that governments tend to be more immediately and generously responsive in providing for the immediate needs of those who are ill. As a practical reality, patients express gratitude for the services received and political support for those providing them. Preventive services are less appealing, the results being reflected in impersonal statistics which indicate that there are fewer or perhaps no patients. An equally important problem is the fact that measures for disease prevention usually require a long period of sustained support and attention before results become apparent. Unfortunately, government officials and donor organizations customarily conceive of plans and budgets in blocks of 3–5 years. Longer-term commitments are uncommon, and with changes in leadership different initiatives are pursued. Even for smallpox eradication, which required comparatively small resources, it proved difficult in most countries to sustain the interest of both national governments and international agencies much beyond 5–6 years.

The Cost to the Developing Countries

For the endemic countries, data regarding the cost of smallpox control programmes are few, and estimates of the expenditure on the care of patients and of the economic losses in productivity due to death or illnss are available only for India. No known data document the cost of rehabilitation for those who were left blind or otherwise handicapped.

In 1967, the cost of smallpox control programmes consisted primarily of expenditure on vaccination, i.e., the cost of vaccine, personnel and transport. For the developing countries, this amounted to about US$0.10 per vaccination performed (World Health Organization, 1966b). From national programme reports, it is estimated that a number equivalent to about 20% of the 2500 million residents of the developing countries was being vaccinated each year. This would suggest that about US$50 million were being expended annually for vaccination (Table 31.1).

The costs of care for those who developed smallpox were computed in a study in India by Ramaiah (1976a), who calculated an average expenditure of US$2.85 per patient. Assuming, as he does (Ramaiah, 1976b), that about 2% of all cases were being reported in India in 1967, the total cost of patient care for that year in India alone would have been US$12 million. Given the fact that India, in 1967, accounted for 64% of all reported cases in the world, it would seem reasonable to estimate the cost of patient care globally at more than US$20 million.

Losses due to diminished economic productivity as a result of death must also be considered. For India, during 1967, they are calculated to have been about US$700 million.

Table 31.1. Estimated cost of smallpox to the developing countries, 1967 (millions of US$)[a]

	India	All developing countries
Smallpox control through vaccination	10	50
Care of smallpox patients	12	>20
Loss from diminished economic productivity	700	>1 000
Total	722	>1 070

[a] Because the most comprehensive data are from India (Ramaiah, 1976a,b; Basu et al., 1979), these are given separately, the figures for all developing countries being extrapolated from those for India. Among a total population of 1079 million persons in the endemic countries in 1967, 513 million (48%) lived in India.

The calculation is based on Ramaiah's analysis (1976a), which employs a life-table approach and defines economic productivity in terms of expected excess of income over consumption during the individual's lifetime. However approximate the calculation, the average loss in economic productivity of about US$825 per death would appear conservative. Extrapolated globally for perhaps 1.5 million deaths which were estimated to have occurred in 1967, it would seem reasonable to assign a value of at least US$1000 million.

Loss of productivity due to the 3–4 weeks of incapacitation associated with illness must also be considered although in India this was found to be small (Ramaiah, 1976a), mainly because a large proportion of cases were in children for whom no loss in productivity was assumed, and, in part, owing to the low productivity of the average worker.

From these data, sketchy as they are, the cost of smallpox to the developing countries in 1967 was substantial indeed, being not less than US$1000 million (Table 31.1).

The Cost to the Industrialized Countries

Almost all industrialized countries spent substantial sums of money for the routine vaccination of their own populations so that, if smallpox was introduced, the disease would not spread widely; international travellers were required to present certificates of vaccination; and at least two countries maintained special hospitals for use should smallpox be introduced.

Only one comprehensive study of the costs of smallpox prevention in an industrialized country has been reported, a study conducted in the USA in 1968 (Sencer & Axnick, 1973). The cost that year to the USA of providing 5.6 million primary vaccinations and 8.6 million revaccinations was calculated to be US$92.8 million—about US$6.50 per vaccination (Table 31.2). Among those vaccinated, 8024 had complications requiring medical attention, 238 were hospitalized, 9 died and 4 were permanently disabled. Other costs were associated with absences from work due to vaccination and vaccination reactions, quarantine services and time lost by the maritime industry in waiting for clearance of vessels. The average annual cost of US$150 million amounted to about US$0.75 per capita for 1968. These data do not permit accurate global estimates of the expenditure by all industrialized countries but, if a cost as low as US$0.25 per capita is assumed for those other than the USA, the annual cost, for 1967, would have been US$350 million.

Table 31.2. Costs associated with smallpox protection in the USA, 1968 (millions of US$)[a]

	Amount
Direct cost for medical services:	
Vaccination	92.8
Treatment of complications	0.7
Indirect costs, loss of productivity:	
Work losses due to vaccination and reactions	41.7
Permanent disability due to complications	0.4
Premature death	0.1
Cost of international traffic surveillance and delays in clearance of vessels	14.5
Total	150.2

[a] From Sencer & Axnick (1973).

Expenditure

Compared to the annual cost of smallpox to the world which, in 1967, was more than US$1350 million, the anticipated expenditures for a 10-year global eradication programme were modest indeed. The Director-General of WHO, in 1966, estimated a need for international assistance of US$4.85 million per year over a 10-year period. He requested that US$2.4 million be appropriated for this purpose in WHO's 1967 budget, although this was accepted by the World Health Assembly by only the narrowest of margins (see Chapter 9).

Ultimately, the costs of the programme were greater than had been anticipated (Table 31.3). International expenditure amounted to US$98 million, about twice what had been foreseen. The endemic countries are believed to have spent no more than twice this amount, about US$200 million.

For all countries, the economic benefits of the programme were substantial as it became possible to stop all preventive measures and to close treatment facilities. The USA, although the largest donor, is estimated to realize in savings the total of all its contributions to the programme every 26 days (Brilliant, 1985).

IMPLICATIONS FOR THE FUTURE

The achievement of smallpox eradication demonstrated the potential of WHO as an organization within which all countries, whatever their beliefs and politics, could cooperate successfully in the pursuit of a

Table 31.3. Expenditure on smallpox eradication, 1967–1979 (US$)[a]

	Estimated expenditure, 1967–1979	% of total
International expenditure		
WHO regular budget	33 565 248	11
WHO Voluntary Fund for Health Promotion	37 643 037	13
Other organs of United Nations system	2 492 328	1
Bilateral assistance	24 269 124	8
Total	97 969 737	33
National expenditure in the endemic countries[a]	200 000 000	67

[a] Based on analysis of financial data from Bangladesh, Ethiopia, India and Indonesia and less complete data from other countries which had endemic smallpox in 1967.

common global objective. It encourages the hope that other challenges might likewise be addressed. By demonstrating how cost-effective a population-wide programme for disease prevention could be, it directed attention to other preventive measures and health programmes which could effectively utilize community-wide strategies. Previously endemic countries, having become aware of the considerable capacity of their own health services when given proper direction and supervision, looked toward new goals. Thus, an important impetus was provided for new initiatives in, for example, immunization, diarrhoeal disease control and the prevention of blindness. This was by far the most significant contribution of smallpox eradication to the shaping of future strategies for the provision of health care.

Global smallpox eradication came at a time when conventional wisdom increasingly held that human pathogens were ecologically so well adapted that the concept of eradication was untenable (Dubos, 1965). However, the demonstration that the eradication of a disease was feasible led a number of scientists to conclude that this very feasibility was the most important lesson to be learned from the programme and to advocate that a similar approach should be taken to other diseases (Stuart-Harris et al., 1982). A number of diseases have been proposed as candidates, and efforts have, in fact, begun to eliminate dracunculiasis (guinea-worm infection) globally and to eradicate poliomyelitis from the Western Hemisphere.

Disease eradication is unquestionably an attractive goal, but the difficulty of its achievement should not be underestimated. It must be borne in mind that when the smallpox eradication programme began, the prospects for its success were more favourable than for any other disease eradication programme that might be envisaged today. The technical feasibility of interrupting the transmission of the smallpox virus had already been demonstrated both in the industrialized countries and in many developing ones; an inexpensive, highly effective vaccine was available; and there was a substantial political commitment to the achievement of the goal that had been set. Nevertheless, however favourable the circumstances, success was by no means a certainty even during the concluding years or even the final months of the programme. Indeed, the gap between success and failure in a number of national programmes was a narrow one, and the issue was often favourably decided by fortuitous and unpredictable political developments and with only marginally adequate resources. It is difficult to conceive of other disease eradication programmes experiencing fewer problems; and if they were technically more difficult or less adequately and universally supported, their success would appear to be doubtful indeed.

The consequences of the failure of an eradication programme must also be weighed. Some have argued that such special efforts as would be required would result, at worst, in better control of the disease. However, the repercussions which followed upon the failure of malaria eradication cannot be ignored. Not only was the judgement and credibility of national and international leadership called into question but a number of assistance agencies decided, as a matter of policy, not to provide resources for another eradication effort. Some agencies, in fact, questioned the desirability of supporting any categorical disease programmes. These views prevailed throughout the smallpox eradication programme, often to its detriment.

Eradication of Other Diseases

The possible eradication of a number of diseases has been considered recently (Stuart-Harris et al., 1982) although, in the enthusiasm and interest, the proper definition of eradication has been deplorably corrupted (see Chapter 9). Some have used the term to refer to the control of a disease to the point at which it is no longer an important public

health problem and some have mistakenly applied the term to programmes intended to prevent hunger or to control accidents and injuries. Here, we refer only to the feasibility of interrupting the transmission of an infectious agent over a geographical area of sufficient size so that control measures may be stopped or greatly reduced, i.e., eradication on a regional or global scale.

The candidate diseases of greatest interest are those in which man is the only host of the pathogen and the pathogens themselves do not survive for long periods in nature or man. The prospects for eradicating diseases which have an animal reservoir—such as yellow fever, rabies or plague—are nil given present technology. Equally problematic are cholera, the vibrio of which can persist for a long time in brackish, polluted waters, and diseases such as tuberculosis and leprosy, of which the mycobacteria can remain latent in man for many decades.

Another important consideration which must be weighed in considering a disease for eradication is obtaining a sufficiently broad and sustained political commitment. Those who decide policy and the allocation of funds must perceive the disease problem to be serious enough to warrant expending additional funds; but, no less, the populations which are most affected must be sufficiently motivated to cooperate. The time required is important as well because, as was noted above, it proved difficult in all countries to sustain an interest in smallpox eradication for longer than about 6 years.

The preventive measures required for eradicating the disease in question must be inexpensive, considering the fact that international support for health programmes has never been substantial and that most developing countries are already hard-pressed to meet the needs of their existing health activities. The smallpox eradication experience must be borne in mind as, despite the relatively small budget it called for and the implications which success had for all countries, the difficulty of having adequate funds available was a major constraint.

Finally, the methods to be used for the eradication of a disease should be comparatively simple to apply and should not require frequent, repeated contacts with individuals in the population. Skilled management in the developing countries is not plentiful, and programmes that require complicated procedures or considerable discretionary judgement are less likely to succeed than simpler ones. Problems can also be anticipated if it is necessary to contact the population on repeated occasions, as would be the case if individual subjects had to be given a drug each day or each week for a period of weeks or months. The cost and discipline required to execute such programmes make them prohibitive in most areas.

The prospects at present for the global eradication of most human diseases are not good. Epidemiological characteristics preclude many from consideration, while the nature and cost of the available technologies rule out others. However, with a growing international interest in prevention programmes and the emergence of new and better vaccines and other technological developments, there is hope that other global eradication programmes may eventually be successfully mounted. During recent years, 4 diseases have been seriously advanced as candidates for global eradication within the foreseeable future: measles (Hopkins et al., 1982; Katz et al., 1983), poliomyelitis (Horstmann et al., 1984), dracunculiasis (Hopkins, 1983b), and yaws (Hopkins, 1976; Burke et al., 1985). In 1985, the Pan American Health Organization approved a regional poliomyelitis eradication programme, the objective of which is the interruption of poliovirus transmission in the Western Hemisphere by 1990. In 1986, a programme for the global elimination of dracunculiasis was approved by the Thirty-ninth World Health Assembly (resolution WHA39.21) although no time limit was established for its accomplishment. The prospects for each of these initiatives are briefly reviewed below.

Measles

The possibility of measles eradication is suggested by the fact that man is the only host of the virus and that a single dose of an inexpensive vaccine provides long-lasting immunity in 90–95% of vaccinated persons. In developing countries, measles is a sufficiently serious disease to warrant an eradication programme. In the industrialized countries, however, complications and deaths associated with measles are so much less frequent that many countries do not now conduct effective control programmes. The wisdom of this policy has to be questioned but, certainly, there is not yet universal interest in the control of the disease, let alone

in its eradication. There are other impediments as well. The measles virus is much more readily transmitted from person to person than was that of smallpox. Not surprisingly, the disease spreads rapidly and widely, and a high proportion of children in developing countries experience measles before they reach 3 years of age. Because the virus spreads so easily and the diagnosis may present difficulties, surveillance–containment measures such as were used in smallpox eradication have not proved to be feasible or effective. To interrupt transmission, it has been calculated (Anderson & May, 1983) that an immunity level greater than 90% will be necessary, a level which is all the more difficult to achieve because vaccination is not possible before the age of 6–12 months, when the child loses its maternal antibody. If there were a vaccine which could be administered at or shortly after birth, the prospects would certainly be better.

Practical evidence that an eradication campaign is premature is provided by the experience in the USA. There, the incidence of measles has been reduced almost to nil but, despite a commitment to interrupt transmission by 1982 and the provision of considerable resources to that end, the measles virus continues to spread.

Poliomyelitis

The feasibility of eradicating poliomyelitis appears greater than that of eradicating measles. Poliomyelitis is more universally accepted as being of sufficient importance to warrant an eradication programme. Man is the only host of the virus and good protection is usually provided by both the inactivated vaccine and the attenuated live vaccine. Many industrialized countries and some developing countries have, in fact, already been successful in interrupting poliovirus transmission, mostly through use of the oral, attenuated vaccine. Some industrialized countries which have used the inactivated vaccine have also been successful.

The decision by the Pan American Health Organization to begin a regional poliomyelitis eradication campaign was preceded by national vaccination campaigns in the Americas in which the inexpensive and easily administered oral vaccine was used. In the early 1970s continuing circulation of poliovirus ceased in North America, and by 1985 the number of reported cases in the Western Hemisphere had diminished to fewer than 1000 a year.

The eradication of poliomyelitis, however, presents a number of special problems. First, the oral vaccine is so thermolabile that refrigeration is required almost to the point of administration, and at least 3 doses are necessary for protection. Vaccination campaigns that must depend upon such a vaccine are inevitably more complex and more difficult than those in which a single dose of thermostable vaccine can be used, as was the case with smallpox. Another matter of concern is the fact that several studies suggest that the oral vaccine is less efficacious in some tropical areas than in temperate climates, although the reasons for this remain unclear. The inactivated vaccine has been suggested as an alternative but it is more costly and requires 2 doses to be given by syringe and needle, a more cumbersome method. A second set of problems concerns the development of surveillance methods by which to detect the presence of circulating poliovirus. Only 1 person among 1000 or more who are infected with the virus manifests paralytic disease, and such cases require confirmation by laboratory examination. The occurrence of paralytic cases signifies that poliovirus is present in an area, but their absence does not necessarily indicate the contrary because it is known that poliovirus can spread over large areas and for an unknown period of time without causing paralytic illness. Confirmation that poliovirus transmission has been interrupted is therefore difficult. A surveillance system for paralytic illness is being developed in the Americas which involves laboratory confirmation of suspected cases and community-wide containment vaccination. The efficacy of this approach in reducing the transmission of the virus and its sensitivity in detecting circulating virus remain to be determined. The experience acquired in the Western Hemisphere will determine the feasibility of eradication in other areas.

Dracunculiasis (guinea-worm infection)

The elimination of dracunculiasis, a parasitic infection, was agreed upon by the Thirty-ninth World Health Assembly, in 1986, as a campaign to be conducted in association with programmes of the International Drinking Water Supply and Sanitation Decade; although the Health Assembly's resolution (WHA39.21) speaks of "elimination", it is

difficult to distinguish the intent of this from that of "eradication". The parasite, *Dracunculus medinensis*, a nematode worm that measures 35–100 cm in length when adult, lives in the skin of man, the female emerging in a painful abscess to discharge tiny larvae when the infected part of the body is immersed in water. The larvae are ingested by a minute freshwater crustacean, *Cyclops*, that serves as an intermediate host, in which they mature and infect man when he swallows water contaminated by the *Cyclops* organisms. Interruption of guinea-worm transmission is reasonably easily and rapidly achieved either by destroying the larval form of the parasite in the water tanks and ponds where people are infected, by filtering or boiling water before drinking it or by preventing patients with infection from entering such bodies of water.

Favouring eradication is the fact that comparatively simple measures have produced a dramatic reduction in incidence and the elimination of infection in many villages and larger areas of Africa and Asia. Moreover, the population at risk is estimated to be no more than 50 million persons, almost all of whom now live in rural areas in a regional belt extending across the middle of Africa and in western India and eastern Pakistan. Finally, the disease itself is a painful, disabling one of concern to the afflicted population, and for surveillance purposes the adult worm is easy to identify.

The principal problems which can be foreseen are those of interesting donor agencies in providing support for the elimination of a tropical disease which is so little known outside the affected countries and of mobilizing national interest and support for the elimination of a disease rarely seen outside rural and often remote areas.

Yaws

Yaws is a treponemal infection, transmitted from person to person, against which widespread control and eradication campaigns were mounted during the 1950s and 1960s (see Chapter 9). A single dose of penicillin effected a rapid cure and these earlier campaigns succeeded in dramatically reducing the incidence of the disease. Initially, it appeared that eradication could be easily and rapidly accomplished, but persistent low-level infections which were difficult to detect resulted in the continuation of transmission. A more concerted effort involving repeated visits to inspect all persons in the afflicted areas was required but, as cases diminished in number, so, too, did both the national and international interest and commitment.

During recent years, there has been a resurgence of yaws in many countries of Africa and some in Asia (*Wkly epidem. rec.*, 1986a) and renewed campaigns have begun in a number of them. Although the eradication of yaws has been proposed as a possible goal, recognition of the extent and magnitude of the problem, of the practical difficulties and of the cost of implementing successful programmes has effectively muted discussion of eradication for the time being.

Conclusion

It is apparent that the successful eradication of smallpox has had important ramifications into other areas of health work, while it also provides illuminating evidence of the need for caution in deciding upon other eradication programmes. Those who were directly engaged in smallpox eradication, and many other health staff as well, gained an understanding of the impact a community-based programme, especially one in prevention, could have, of its remarkable cost-benefit implications and of the considerable human and financial resources which could be mobilized for such an effort. Many of these persons, both in developing and in industrialized countries, are now applying that understanding in public health practice. The establishment of specific, measurable, practical goals and their use in management have begun to be introduced into national health programme objectives and into community-based health initiatives. Surveillance and sample survey techniques elaborated in the course of smallpox eradication have begun to be employed increasingly in health programme management. Throughout the world, more emphasis is being placed on programmes for disease prevention and health promotion, in respect of both communicable and non-communicable diseases, although the need for such programmes is still vastly greater than the effort that is being expended upon them.

WHO, whose role in smallpox eradication was so vital, offers a unique, although as yet not fully realized potential, for promoting these new and growing efforts. It is an organization which demonstrably can catalyse achievements far out of proportion to the

financial resources it commands. The extent to which it is successful will depend upon the confidence which its Member States place upon it, on its effectiveness in enunciating clear and measurable objectives and in mobilizing support for their realization, on the number and competence of its professional staff, and on its ability to set aside extraneous political questions. Its ability to respond appropriately to challenges old and new will be decisive in its task of helping all the people of the world to the attainment of the highest possible level of health.

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